Novel Oral Iron Therapies for Iron Deficiency Anemia in Chronic Kidney Disease

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Iron deficiency anemia (IDA) is a frequent complication of chronic kidney disease (CKD) and is associated with adverse outcomes in these patients. Patients with CKD and IDA remain largely undertreated. Conventional oral iron agents are insufficiently effective due to poor absorption and cause gastrointestinal side effects; thus, novel oral iron preparations are needed. This article covers current treatment guidelines for patients with anemia and CKD and clinical trial data for iron-repletion agents currently in use, as well as for novel oral iron therapies in development. Ferric citrate, a novel oral iron-repletion agent approved for patients with non-dialysis-dependent CKD and IDA, demonstrated improvements in hemoglobin levels and iron parameters, with good tolerability in patients with non-dialysis-dependent CKD. When used as a phosphate binder, ferric citrate also improves hemoglobin and iron parameters in dialysis-dependent CKD, but additional trials are needed to evaluate its efficacy as an iron-repletion agent in this setting. Other novel oral iron preparations in development for IDA in patients with CKD include ferric maltol, which is approved in Europe and the United States for IDA in adult patients, and sucrosomial iron, which has been evaluated in IDA associated with CKD and several other clinical settings.

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ANEMIA IN CHRONIC KIDNEY DISEASE

Anemia occurs frequently in patients with CKD and its prevalence increases as CKD progresses.[1,2] According to Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guidelines, a diagnosis of anemia in adults and children >15 years with CKD is defined as a hemoglobin (Hb) concentration <13.0 g/dL in males and <12.0 g/dL in females.[1] Key mechanisms for the pathogenesis of anemia in CKD involve a relative deficiency of erythropoietin, iron deficiency and maldistribution,[3] increased blood loss, and shortened erythrocyte lifespan.[4]

The prevalence of iron deficiency anemia (IDA) increases with worsening CKD; in a large cross-sectional survey ($N = 5222$), Hb concentrations <12 g/dL were observed in approximately one quarter of patients with glomerular filtration rate ≥60 mL/min/1.73 m^2 vs approximately three quarters of patients with glomerular filtration rate <15 mL/min/1.73 m^2.[5] Causes of absolute iron deficiency include reduced iron intake, as well as increased blood loss from overt or occult gastrointestinal (GI) losses, surgical procedures, or associated with hemodialysis procedures.[4,6] Iron maldistribution is caused by increases in levels of hepcidin, a regulator of iron homeostasis. The increase in hepcidin levels caused by chronic inflammation in CKD and decreased renal clearance of hepcidin results in occlusion and internalization of ferroportin (a cellular iron transporter), a decrease in the absorption of iron from the intestine, and a reduction of iron release from macrophages and the liver, resulting in a decrease in the available iron for erythropoiesis.[7,8] Functional iron deficiency (related to iron requirements of accelerated erythropoiesis) is the inability of iron delivery to keep up with rapid erythropoiesis induced by therapeutic doses of erythropoietin and can limit the response to erythropoietin therapy[9]; mechanistically, both iron maldistribution (elevated hepcidin blocking the release of iron from cells) and absolute iron deficiency can contribute to the functional deficiency. Absolute iron deficiency (eg, blood losses), iron maldistribution, and functional iron deficiency can coexist in patients with CKD.[10]

KDIGO recommends using serum ferritin and transferrin saturation (TSAT) to assess iron status in patients with CKD. Although serum ferritin levels ≤30 ng/mL typically indicate severe iron deficiency in CKD patients, ferritin levels are increased by inflammation and even levels higher than 30 ng/mL may mask iron deficiency in these patients.[1] Empirically, ferritin levels ≥300 ng/mL in patients with dialysis-dependent CKD (DD-CKD) and ferritin levels ≥100 ng/mL in patients with NDD-CKD are suggestive of sufficient iron stores. In a national survey conducted between 1988 and 2004, approximately 58%-73% of all patients with non-dialysis-dependent CKD (NDD-CKD) were found to be iron deficient with serum ferritin <100 ng/mL or TSAT <20%.[11]

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CURRENT TREATMENT OF ANEMIA IN CKD

The current clinical management of anemia in CKD includes erythropoiesis-stimulating agents (ESAs) and iron replacement therapy with oral and intravenous (IV) agents. Red blood cell transfusions are often used as a last resort mainly in urgent circumstances.[1]

Use of ESAs helps avoid transfusions and may improve anemia-related symptoms when used to achieve Hb targets of 10-12 g/dL. In contrast, when the Hb target is >13 g/dL ESAs are associated with serious adverse effects such as stroke, vascular access loss, and death.[3,12] Risks of cardiovascular events and death are further increased in patients treated with Hb levels >13 g/dL.[3,13] KDIGO guidelines suggest addressing all correctable causes of anemia prior to ESA use,[1] and considering ESA use only if Hb ≤10.0 g/dL.

Optimal anemia treatment with ESAs requires the patient to be iron replete. Roughly 10%-20% of patients are nonresponsive to ESAs,[3] commonly because of iron deficiency.[1] Frequently, IV iron is given either prior to ESA initiation or shortly after, as the patient's iron stores and absorption are usually not adequate to meet the demands of accelerated erythropoiesis. Iron supplementation in patients receiving ESAs helps reduce ESA dose,[1,14] therefore decreasing their potential adverse effects.[12]

Iron Therapy

In adult patients with anemia not on ESA or iron therapy and with TSAT ≤30% and ferritin ≤500 ng/mL, KDIGO guidelines recommend a trial of IV iron (DD-CKD) or a 1-3 month trial of oral iron therapy (NDD-CKD). For patients on ESAs with a TSAT of ≤30% and ferritin ≤500 ng/mL and for whom an increase in Hb levels or a reduction in ESA dosage is desired, a trial of IV iron (DD-CKD) or a 1-3 month trial of oral iron therapy (NDD-CKD) is recommended.[1]

However, clinical evidence supporting these recommendations is sparse[15]; recent trials suggest the need for redefining iron status targets for initiating iron therapy in this patient population.[14] Ferritin and TSAT levels vary widely in patients with CKD,[16] and differences in interpretation of KDIGO guidelines as well as IDA-screening practices contribute to a great variability in the cutoffs used to diagnose IDA in patients with CKD.[17] It should also be noted that these guidelines preceded the development of newer and more effective oral iron repletion agents (such as ferric citrate [FC]).

CLINICAL SUMMARY

- Patients with iron deficiency anemia (IDA) and chronic kidney disease (CKD) remain undertreated; conventional oral iron agents historically have been insufficiently effective due to poor iron absorption and gastrointestinal adverse effects, and their effectiveness lessens as the disease advances.
- Ferric citrate, approved for the IDA in patients with non-dialysis-dependent CKD (NDD-CKD), significantly improves hemoglobin response and iron parameters, with low rates of serious adverse events like hypophosphatemia, and treatment-related discontinuations.
- Ferric maltol, approved in Europe and the United States for IDA in adult patients, and sucrosomial iron preparations have been evaluated clinically and have shown encouraging results in patients with NDD-CKD.
- Additional trials are needed to assess the long-term effects of ferric citrate in NDD-CKD and the role of ferric citrate as an iron-repletion agent in patients with dialysis-dependent CKD.

TRADITIONAL ORAL IRON FORMULATIONS

Traditional oral iron preparations are usually cheaper and easier to administer than IV formulations; however, high rates of gastrointestinal adverse effects and low bioavailability from poor intestinal absorption may limit their efficacy. Among traditional oral iron preparations used to treat anemia in patients with CKD (Table 1), ferrous sulfate (65 mg of elemental iron per 325 mg tablet) is considered a standard treatment.[18,19] However, the low efficacy of iron absorption is a concern with conventional oral preparations, considering the magnitude of iron repletion needed, particularly in patients on hemodialysis,[4,13] who may lose up to 2000 mg of iron per year through physiological and pathological losses (eg, hemodialysis procedure or GI procedure). Absorption of ferrous iron preparations is usually 10%-15%, while that of ferric iron preparations may be 3-4 times lower, because of the physiology of iron absorption in the intestine (Fig 1) and the poor solubility of ferric iron in the alkaline environment of the gut.[21] GI adverse events (AEs) such as nausea, constipation, diarrhea, and dyspepsia limit the tolerability of ferrous oral iron preparations, resulting in lower doses of elemental iron being delivered and poor patient compliance.[13,21,22] In a systematic review, almost a third of 3271 patients who received oral ferrous sulfate reported AEs, most commonly GI-related.[23]

IV IRON FORMULATIONS

IV iron can be administered in larger doses by circumventing tolerability issues associated with oral iron preparations.[19] Multiple randomized clinical trials over the last decade have demonstrated the superiority of IV iron preparations over traditional oral preparations in improving iron parameters (Tables 2 and 3) and reducing ESA use, particularly in patients with DD-CKD (Table 3)[18,19]; these data form the basis of guidelines recommending IV iron in patients with CKD.[1]

Despite improved efficacy, the use of IV iron is associated with concerns about AEs,[1] including serious AEs (SAEs), such as anaphylaxis, infections, and cardiovascular events/disease among patients with NDD-CKD and IDA.[23,30,38] In the REVOKE trial (randomized trial to evaluate intravenous and oral iron in chronic kidney disease), the risk of SAEs was shown to be higher for IV vs oral iron repletion, with an adjusted incidence rate ratio of 1.60 (95% confidence interval [CI] 1.28-2.00, $P < 0.0001$).[15] These findings contrast with those

Table 1. List of Oral Iron Agents Used for Treating Anemia in Patients With CKD

Agent	Elemental Iron per Tablet	Total Salt Content per Tablet	Recommended Dosage
Ferric citrate or FC (Auryxia)	210 mg	1 g	3 tablets a day (630 mg elemental iron) with meals for IDA in CKD
Ferric citrate hydrate or FCH (Riona)	45 mg	250 mg	500 mg × 3 times a day for hyperphosphatemia in CKD
Ferric citrate (Nephoxil)	105 mg	500 mg	N/A
Ferric maltol (Feraccru)	30 mg	30 mg	30 mg twice daily
Ferrous sulfate (generic)	65 mg	325 mg	1000 mg/d (200 mg/d elemental iron) for IDA in CKD
Ferrous fumarate (Ferro-Sequels; Slow FE, Apo-Ferrous Gluconate)	106 mg	325 mg	600 mg/d (200 mg/d elemental iron) for IDA in CKD
Ferrous gluconate (Fergon)	37.5 mg	325 mg	1600 mg/d (200 mg/d elemental iron) for IDA in CKD
Liposomal iron (Ferrolip)	30 mg	30 mg	30 mg/d (for IDA)
Heme iron polypeptide (Proferrin)	12 mg	12 mg	3 or 4 tablets/d (for IDA in CKD)

Abbreviations: CKD, chronic kidney disease; IDA, iron deficiency anemia; N/A, not available.

of the FIND-CKD trial (Ferinject Assessment in patients with IDA and NDD-CKD), which found similar rates of infections and cardiovascular events between the IV and oral treatment groups,[29] even after adjusting for differences in AE reporting between the 2 trials.[39] This may be explained by differences in the patient population and the use of different IV iron preparations in the REVOKE (iron sucrose) and FIND-CKD (ferric carboxymaltose) trials. Increased rates of SAEs also have been reported with high- vs low-dose IV iron[13]; however, results of the randomized PIVOTAL study (randomized trial comparing proactive, high-dose versus reactive, low-dose intravenous iron supplementation in hemodialysis), which compared high- vs low-dose IV iron in patients undergoing dialysis ($N = 2141$), found no difference in the rate of SAEs between the 2 treatment groups.[40] Certain IV iron preparations (ferric carboxymaltose, iron polymaltose, and saccharated iron oxide) are associated with increased risk of hypophosphatemia in patients with CKD, possibly mediated by increased levels of intact fibroblast growth factor 23 (iFGF23, the most bioactive form) and subsequent increased urinary phosphate excretion after infusion.[41] KDIGO guidelines urge caution when using IV iron in patients with NDD-CKD.[14]

When evaluating the benefits and risks of iron repletion therapy, IV iron sparing and ESA-sparing strategies are important to consider. Effective oral agents are needed that deliver sufficient elemental iron doses without the added GI risks.

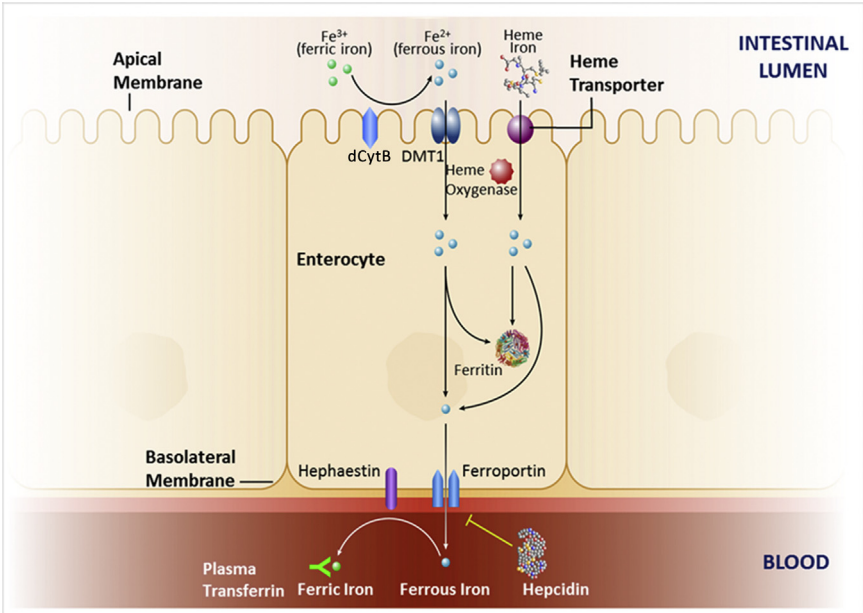

Figure 1. Enterocyte-based iron trafficking. Ferric iron is reduced to ferrous iron by duodenal cytochrome b (dCytB) and ferrous iron is transported by the divalent metal-ion transporter into enterocytes. Here, ferrous iron is stored bound to ferritin. Ferrous iron is exported via ferroportin, whose levels are modulated by hepcidin. In the blood, ferrous iron is oxidized back to ferric iron and bound to transferrin for transport. Modified from Panwar and Gutierrez, *Seminars in Nephrology;* 2016;36(4):252-261, Copyright 2016, with permission from Elsevier.[20]

Table 2. Iron Preparations in the Treatment of Anemia in NDD-CKD: Efficacy Results From Randomized Controlled Trials Published From 2008 to 2018

Reference	Agents	Patient Population	Dosage and Duration	Changes in Iron Parameters: TSAT (%) and Ferritin (ng/mL) (BL to End of FU)	Changes in Hb g/dL) (BL to End of FU)	Notes on ESA Usage
Spinowitz 2008[24]	IV ferumoxytol vs ferrous fumarate	CKD stage 1-5, TSAT ≤30%, ferritin ≤600 ng/mL, Hb ≤11.0 g/dL $N = 228$; $N = 76$	2× 510 mg doses within 5 ± 3 days; FU at day 35 200 mg elemental iron/d on empty stomach, 21 days treatment; FU at day 35	Mean change (±SD) in TSAT: 9.8 ± 9.2%, 1.3 ± 6.4%, $P < 0.0001$ Mean change (±SD) in ferritin: 381.7 ± 278.6 ng/mL, 6.9 ± 60.1 ng/mL, $P < .0001$	Mean increase in Hb: 0.82 ± 1.24 vs 0.16 ± 1.02 g/dL, $P < 0.0001$ Proportion of patients achieving an increase in Hb of ≥1.0 g/dL: 39.0% vs 18.4%	Yes (36%; 43%)* Ferumoxytol resulted in significant Hb increases over placebo in both ESA treated and nontreated patients; mean Hb increase was higher in ESA-treated patients
Qunibi 2011[25]	IV FCM vs oral iron sulfate	eGFR ≤45 mL/min/1.73 m^2, Hb ≤11.0 g/dL, TSAT ≤25%, ferritin ≤300 ng/mL $N = 152$; $N = 103$	3× 1000 mg infusions and 2 additional infusions pif TSAT <30% and ferritin <500 ng/mL; FU at 8 weeks 195 mg elemental iron/d before meals, 56 days treatment; FU at 8 weeks	Mean change (±SD) in TSAT: 12.1 ± 8.8% vs 7.0 ± 10.3%, $P < 0.001$ Mean change (±SD) in ferritin: 358.8 ± 178.4 ng/mL, 25.8 ± 49.4 ng/mL, $P < 0.001$	Proportion of patients achieving an increase in Hb of ≥1.0 g/dL: 60.4% vs 34.7%, $P < 0.001$	Yes (24%; 25%)* FCM benefited both ESA-treated and nontreated patients; more ESA-treated patients achieved Hb increases
Nagaraju 2013[26]	IV iron sucrose vs oral heme iron polypeptide	(eGFR) ≤60 mL/min/1.73 m^2, Hb = 9.0-12.0 g/dL (females) and 9.0-13.5 g/dL (males); serum ferritin <100 ng/mL; ferritin <100 ng/mL or TSAT <20% $N = 22$; $N = 18$	200 mg infusions monthly for 6 months; FU at 6 months 33 mg elemental iron/d, for 6 months; FU at 6 months	Change in TSAT: 16.5% (BL) to 21.5% (FU) vs 17% (BL) to 21.5% (FU) ($P < 0.001$) Change in ferritin: 67 ng/mL (BL) to 244 ng/mL (FU) vs 71 ng/mL (BL) to 85.5 ng/mL (FU)	10.85 g/dL (BL) to 11.3 g/dL (FU) 11.05 g/dL (BL) to 11.7 g/dL (FU)	Yes (32%; 33%)† No significant changes in ESA use were observed in either group at 6 months
Charytan 2013[27]	IV FCM vs standard medical care (investigator determined, oral or IV iron)	NDD-CKD patients; Hb ≤11.5 g/dL, TSAT ≤30% and ferritin ≤300 ng/mL (no IV iron within 1 month of study) $N = 204$; $N = 212$	Single dose of 15 mg/kg up to a maximum of 1000 mg IV. FU 30 days Dosing as determined by investigator/physician. FU 30 days	Mean change (±SD) in TSAT: 10.02 ± 8.87% vs 4.93 ± 12.74% ($P \leq 0.001$) Mean change (±SD) in ferritin: 295.59 ± 150.78 ng/mL vs 110.58 ± 153.27 ng/mL ($P \leq 0.001$)	Proportion of patients achieving an increase in Hb of ≥1.0 g/dL: 27.2% vs 20.2% Mean increase in Hb: 0.55 ± 0.92 g/dL vs 0.31 ± 0.85 g/dL ($P = 0.008$)	Yes (28%; 31%) (stable dose postrandomization)

(*Continued*)

Table 2. Iron Preparations in the Treatment of Anemia in NDD-CKD: Efficacy Results From Randomized Controlled Trials Published From 2008 to 2018 (*Continued*)

Reference	Agents	Patient Population	Dosage and Duration	Changes in Iron Parameters: TSAT (%) and Ferritin (ng/mL) (BL to End of FU)	Changes in Hb g/dL) (BL to End of FU)	Notes on ESA Usage
Onken 2014[28]; REPAIR-IDA	IV FCM vs IV iron sucrose	eGFR <60 mL/min/1.73 m^2, Hb ≤11.5 g/dL; ferritin <100 ng/mL or ferritin ≤300 ng/mL and TSAT ≤30% $N = 1276$; $N = 1285$	2× doses of FCM in 1 week 200 mg iron sucrose up to 5 infusions in 14 days FU 56 days	Mean increases in ferritin and TSAT were significantly greater in the FCM group compared to the iron sucrose group	Proportion of patients achieving an increase in Hb of ≥1.0 g/dL: 48.6% vs 41.0% (95% CI 3.6-11.6) Mean increase in Hb: 1.13 ± 1.04 g/dL vs 0.92 ± 0.92 g/dL	Yes: stable ESA for 4 weeks prior to randomization (18%; 18%) Benefit from both treatments was similar for ESA-treated and non-ESA-treated patients
MacDougall 2014[29]; FIND-CKD	IV FCM vs oral ferrous sulfate	NDD-CKD (GFR <60 mL/min/m^2); Hb 9-11 g/dL; ferritin <100 ng/mL or ferritin ≤200 ng/mL and TSAT <20% $N = 153$; $N = 152$; $N = 308$	High ferritin group: initial dose of 1000 mg IV FCM, then 500 mg IV iron every 4 weeks for 48 weeks Low ferritin group: initial dose of 200 mg IV FCM, then 200 mg IV iron every 4 weeks for 48 weeks 100 mg × 2 times daily (elemental iron) 52 weeks FU: 52 weeks or 12 months	High ferritin group: LS mean change (SE) in TSAT: 15.8 (1.3) %, $P = 0.20$ LS mean change (SE) from baseline for ferritin: 451 (10) ng/mL, $P < 0.001$ vs oral iron Low ferritin group: LS mean change (SE) in TSAT: 8.5 (1.3)%, $P = 0.001$ LS mean change (SE) in ferritin: 81 (11) ng/mL, $P < 0.001$ vs oral iron LS mean change (SE) in TSAT: 13.8 (1.0)% LS mean change (SE) in ferritin: 137 (8) ng/mL	A greater proportion of patients achieved an Hb increase ≥1 g/dL with high-ferritin FCM vs oral iron (HR: 2.04; 95% CI 1.52-2.72; $P < 0.001$) High ferritin group: LS mean change (SE) from BL: 1.4 (0.1) g/dL, $P = 0.014$ vs oral iron Low ferritin group: LS mean change (SE) from BL: 0.9 (0.1) g/dL, $P = 0.26$ vs oral iron LS mean change (SE) from BL: 1.0 (0.1) g/dL	No‡
Agarwal 2015[30]; REVOKE	IV iron sucrose vs oral ferrous sulfate	eGFR between >20 and ≤60 mL/min/1.73 m^2; Hb <12 g/dL and ferritin <100 ng/mL or TSAT <25% $N = 67$; $N = 69$	5× infusions of 200 mg IV iron sucrose at weeks 0, 2, 4, 6, and 8 after randomization 200 mg elemental iron/day for 8 weeks FU = 24 months	Serum ferritin concentration was significantly higher in the IV iron group only from baseline to 6 months No statistically significant difference in TSAT between groups during FU§	Hemoglobin levels improved over time in both groups, and no statistically significant difference between mean levels in the treatment groups was noted during FU§	Yes (9%; 7%) The average ESA use over the course of 2 years was similar in the 2 groups

(*Continued*)

Table 2. Iron Preparations in the Treatment of Anemia in NDD-CKD: Efficacy Results From Randomized Controlled Trials Published From 2008 to 2018 (*Continued*)

Reference	Agents	Patient Population	Dosage and Duration	Changes in Iron Parameters: TSAT (%) and Ferritin (ng/mL) (BL to End of FU)	Changes in Hb g/dL) (BL to End of FU)	Notes on ESA Usage
Kalra 2016[31]	IV iron isomaltoside 1000 vs oral ferrous sulfate	eGFR between 15 and 59 mL/min/1.73 m^2 Hb <11.0 g/dL, either or both serum ferritin <200 ng/mL and TSAT <20%; no ESA treatment in the last 8 weeks $N = 233$; $N = 118$	IV iron calculated by Ganzoni's formula (maximum of 1000 mg iron per dose or IV bolus injections of 500 mg iron until full repletion achieved) 200 mg elemental iron/d for 8 weeks	Statistically significant larger increase in serum ferritin and TSAT concentration from baseline to weeks 1, 2, 4, and 8 in the IV iron group compared with oral iron group ($P < 0.001$ for serum ferritin; $P = 0.004$ at week 8 for TSAT)§	Statistically significant larger increase in Hb concentration from baseline to week 8 in IV iron group compared with oral iron group ($P < 0.001$)§	No‖
Pisani 2015[32]	IV iron gluconate vs oral pyrophosphate liposomal iron	CKD stage 3-5: eGFR ≤60 mL/min/ 1.73 m^2, not on dialysis; Hb ≤12 g/ dL, ferritin ≤100 ng/ mL, TSAT ≤25% $N = 33$; $N = 66$	8 × 125 mg infusions IV iron gluconate weekly over 3 months, 30 mg/day for 3 months	TSAT from 17.0 ± 2.1 to 21.5 ± 5.2; $P < 0.05$ vs BL Ferritin from 67.7 ± 31.6 to 238.5 ± 49.7; $P < 0.05$ vs BL TSAT from 16.5 ± 2.2 to 18.3 ± 4.3; $P < 0.05$ vs IV iron Ferritin from 71.4 ± 23.7 to 85.5 ± 31.3; $P < 0.05$ vs IV iron	Mean increases in Hb levels from BL to 3 months were 9.3% and 5.6% Proportion of patients achieving an increase in Hb of ≥0.6 g/dL at 3 months: 56.2% vs 43.5%, $P < 0.05$	Yes (4%; 5%)¶ ESA dose not changed during experimental period

Abbreviations: BL, baseline; CI, confidence interval; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; ESA, erythrocyte-stimulating agent; FC, ferric citrate; FCH, ferric citrate hydrate; FCM, ferric carboxymaltose; FU, follow-up; Hb, hemoglobin; HR, hazard ratio; IDA, iron deficiency anemia; IV, intravenous; LS, least squares of the mean; NDD-CKD, non-dialysis-dependent CKD; SD, standard deviation; SE, standard error; TSAT, transferrin saturation.
*Patients receiving ESA to be on stable dosage; patients were precluded from starting ESA during study.
†If the participant was being treated with an ESA, the medication was continued and the dose was adjusted by the blinded study investigator to maintain Hb from 10.0 to 12.0 g/dL. If the participant was not on an ESA at study entry, once the participant was iron replete (TSAT 20%-50% and ferritin 100-500 ng/mL), if the Hb was <10.0 g/dL, an ESA was started.
‡No ESA or no dose change for randomized period.
§Data not available in a format similar to other studies and therefore are not included here.
‖During the first 8 weeks, patients were not to receive ESAs, blood transfusion, or any anemia therapy (after which, was permitted if the Hb was <10 g/dL).
¶If Hb values resulted in >13 g/dL, ESA dosage was reduced by 25%; similarly, if Hb values resulted in <10 g/dL, ESA dosage was increased by 25%.

Table 3. Iron Preparations in the Treatment of Anemia in DD-CKD: Efficacy Results From Randomized Controlled Trials Published From 2008 to 2018

Agent Study/ Reference	Agents	Patient Population	Dosage/Duration	Changes in Iron Parameters: TSAT (%) and Ferritin (ng/mL) (BL to End of FU)	Changes in Hb (g/dL) (BL to End of FU)	Notes on ESA Usage
Li and Wang 2008[33]	IV iron sucrose vs oral ferrous succinate	Patients on maintenance peritoneal dialysis with stable condition for at least 1 month, ferritin <500 ng/mL, TSAT<30%, Hb 6.0-9.0 g/dL, and hematocrit 18%-27% $N = 26$; $N = 20$	200 mg IV iron sucrose after dialysis once a week for 4 weeks and then once in 2 weeks until week 8 200 mg oral ferrous succinate thrice a day (210 mg elemental iron) taken without food for 8 weeks	Mean change (±SD) in TSAT: 93.9 ± 26.7, 33.6 ± 45.2 ($P < 0.05$) Mean change (±SD) in ferritin: 326.8 ± 80.1 ng/mL, 170.9 ± 71.2 ng/mL ($P < 0.05$)	Proportion of patients achieving an increase in Hb of ≥1.5 g/dL: 94.8% vs 55.0%, $P < 0.05$ Mean increase in Hb: 3.41 ± 1.65 g/dL vs 2.21 ± 1.67 g/dL ($P < 0.05$)	Yes: all patients received EPO After 8 weeks, the mean EPO dose in the IV iron group was significantly lower than that in the oral iron group
Li and Wang 2008[34]	IV iron sucrose vs oral ferrous succinate	Patients on maintenance hemodialysis (2-3 times a week), serum ferritin <500 ng/mL, TSAT <30%, Hb 6.0-9.0 g/dL $N = 70$; $N = 66$	100 mg IV iron sucrose after dialysis twice a week for 8 weeks and once a week until week 12 200 mg oral ferrous succinate thrice a day (210 mg elemental iron) taken without food for 12 weeks	Mean change (±SD) in TSAT: 94.1 ± 86.3, 33.6 ± 47.5 ($P < 0.05$) Mean change (±SD) in ferritin: 386.3 ± 380.8 ng/mL, 187.9 ± 272.3 ng/mL ($P < 0.05$)	Mean increase in Hb: 2.41 ± 1.79 g/dL vs 1.21 ± 1.65 g/dL ($P < 0.05$)	Yes: all patients received EPO After 12 weeks, the mean EPO dose in the IV iron group was significantly lower than that in the oral iron group
Kapoian et al 2008[35]; DRIVE 2 study: 6-week observational extension of the DRIVE study	IV ferric gluconate vs no iron	Patients on hemodialysis for ≥90 days, ferritin 500-1200 ng/mL, TSAT ≤25%, and Hb ≤11.0 g/dL Stable dose of ESAs $N = 56$; $N = 56$	1 g of IV ferric gluconate administered in eight 125-mg doses over 6 weeks; IV iron dose as clinically indicated from week 6 to week 12 No iron for first 6 weeks; IV iron dose as clinically indicated from week 6 to week 12 FU at the end of observational period of 12 weeks	TSAT and serum ferritin levels remained higher in the intravenous ferric gluconate group than in the control group ($P < 0.001$, and $P = 0.014$, respectively)	Hemoglobin levels remained higher in the intravenous ferric gluconate group than in the control group ($P = 0.062$)	Yes, all patients received ESAs Patients in the IV iron group required significantly lower ESA doses against baseline (−7527 ± 18,021 IU/wk, $P = 0.003$) compared with control

(*Continued*)

Table 3. Iron Preparations in the Treatment of Anemia in DD-CKD: Efficacy Results From Randomized Controlled Trials Published From 2008 to 2018 (*Continued*)

Agent Study/ Reference	Agents	Patient Population	Dosage/Duration	Changes in Iron Parameters: TSAT (%) and Ferritin (ng/mL) (BL to End of FU)	Changes in Hb (g/dL) (BL to End of FU)	Notes on ESA Usage
Provenzano 2009[36]	IV ferumoxytol vs oral ferrous fumarate	Patients with stage 5 CKD, on hemodialysis and stable ESAs Hb ≤11.5 g/dL, TSAT ≤30%, serum ferritin ≤600 ng/mL $N = 114$; $N = 116$	2× 510 mg IV ferumoxytol within 5 ± 3 days. Follow-up at day 35 200 mg elemental iron/day 21 days treatment; FU at day 35	Mean (±SD) change in TSAT: 6.44 ± 12.59% vs 0.55 ± 8.34%, $P < 0.0001$. Mean increase in ferritin: 233.9 ± 206.95 ng/mL vs −59.23 ± 106.22 ng/mL, $P < 0.0001$	Mean increase in Hb: 1.02 ± 1.13 g/dL vs 0.46 ± 1.06 g/dL ($P = 0.0002$) Proportion of patients achieving an increase in Hb of ≥1.0 g/dL: 49.0% vs 25.0%, $P = 0.0002$	Yes, all patients received EPO
Charytan 2013[27]	IV ferric carboxymaltose vs standard medical care (investigator determined, oral or IV iron)	Patients on hemodialysis for the last 6 months not needing repletion therapy Hb ≤12.5 g/dL, TSAT ≤30%, and ferritin ≤500 ng/mL $N = 50$; $N = 47$	200 mg bolus IV ferric carboxymaltose 30-60 min into dialysis session. Follow-up 30 days Dosing as determined by investigator/ physician. FU 30 days	Mean change (±SD) in TSAT: 2.55 ± 15.26% vs 5.80 ± 13.84% Mean change (±SD) in ferritin: 15.87 ± 106.60 ng/mL vs 71.77 ± 105.57 ng/mL ($P = 0.013$)	Proportion of patients achieving an increase in Hb of ≥1.0 g/dL: 19.1% vs 30.4% Mean increase in Hb: 0.22 ± 0.89 g/dL vs 0.42 ± 1.00 g/dL, $P = 0.299$	Almost all patients received ESAs
Bhandari 2015[37]	IV iron isomaltoside 1000 vs IV iron sucrose	Patients on hemodialysis for ≥90 days, Hb between 9.5 and 12.5 g/dL, ferritin <800 ng/mL, TSAT <35%, ESAs at stable dose for prior 4 weeks $N = 234$; $N = 117$	Cumulative dose of 500 mg iron Single IV dose of iron isomaltoside 1000 bolus of 500 mg or split dose IV iron sucrose, 100 mg at BL, 200 mg at weeks 2 and 4 FU 6 weeks	There was an increase in serum iron and TSAT concentration from baseline to week 6 in both groups; however, no statistically significant changes were observed between the treatment groups*	Majority of patients in either group were able to maintain Hb between 9.5 and 12.5 g/dL at week 6 No statistically significant change in Hb concentrations between groups*	Treatment with ESA stable during trial

Abbreviations: BL, baseline; CKD, chronic kidney disease; DD-CKD, dialysis-dependent CKD; EPO, epoetin alfa; ESA, erythrocyte-stimulating agent; FU, follow-up; Hb, hemoglobin; IV, intravenous; SD, standard deviation; TSAT, transferrin saturation.
*Data not available in a format similar to other studies and therefore are not included here.

NOVEL ORAL IRON THERAPIES

Ferric Citrate

Chemical Properties. Pharmaceutical grade FC is an oral, insoluble, aluminum-free, calcium-free, ferric iron-based agent that was first evaluated as a phosphate binder in patients with DD-CKD. When in solution, the citrate anions in FC covalently coordinate with the ferric iron, forming an FC coordination complex, which masks the iron from water and maintains the iron in solution. FC coordination complexes inhibit ferric iron precipitation, thereby increasing the pool of soluble ferric iron available for iron absorption.[42] FC was soluble over a broad pH range, forming oligomeric complexes in low pH conditions, and mononuclear complexes in higher pH conditions.[42] The ability of FC to form oligomeric complexes at low pH likely contributes to its property of forming insoluble complexes with phosphate ions in the acidic environment of the stomach, and enables dietary phosphate sequestration.[43,44] On the other hand, its property of forming soluble mononuclear complexes in high pH likely enhances ferric ion absorption in the alkaline milieu of the duodenum.

In contrast, early chemical studies of FC used commercial grade FC or CGFC, also known as iron(+3), *x* (1,2,3-propanetricarboxylic acid, 2-hydroxy-), *y* (H_2O). The FC composition of CGFC varies, in that it has variable molar ratios of ferric iron to citrate (Fig 2A) and different amounts of hydration.[42] Pharmaceutical grade FC is the active ingredient of Auryxia, Riona, or Nephoxil (depending on the region), each formulation providing different amounts of elemental iron (Fig 2B; Table 1).

Each 1 g tablet of FC (Auryxia) contains 210 mg of elemental ferric iron, which is converted into ferrous iron by duodenal cytochrome b and ascorbate in the GI tract (Fig 1). Iron can be stored in enterocytes bound to ferritin,[45,46] but if required is exported into the blood via ferroportin, whose levels are modulated by hepcidin.[45] After transport through enterocytes into blood, oxidized ferric iron binds to plasma transferrin and can be incorporated into Hb (Fig 1).

Approvals and Indications. Based on favorable results from the initial evaluation of FC as a phosphate binder in adults with DD-CKD,[47,48] FC (Auryxia) received US Food and Drug Administration (US FDA) approval for this indication in 2014.[49] In addition to binding phosphate, FC was shown to improve iron parameters in DD-CKD.[48,50] FC was then evaluated as an iron repletion

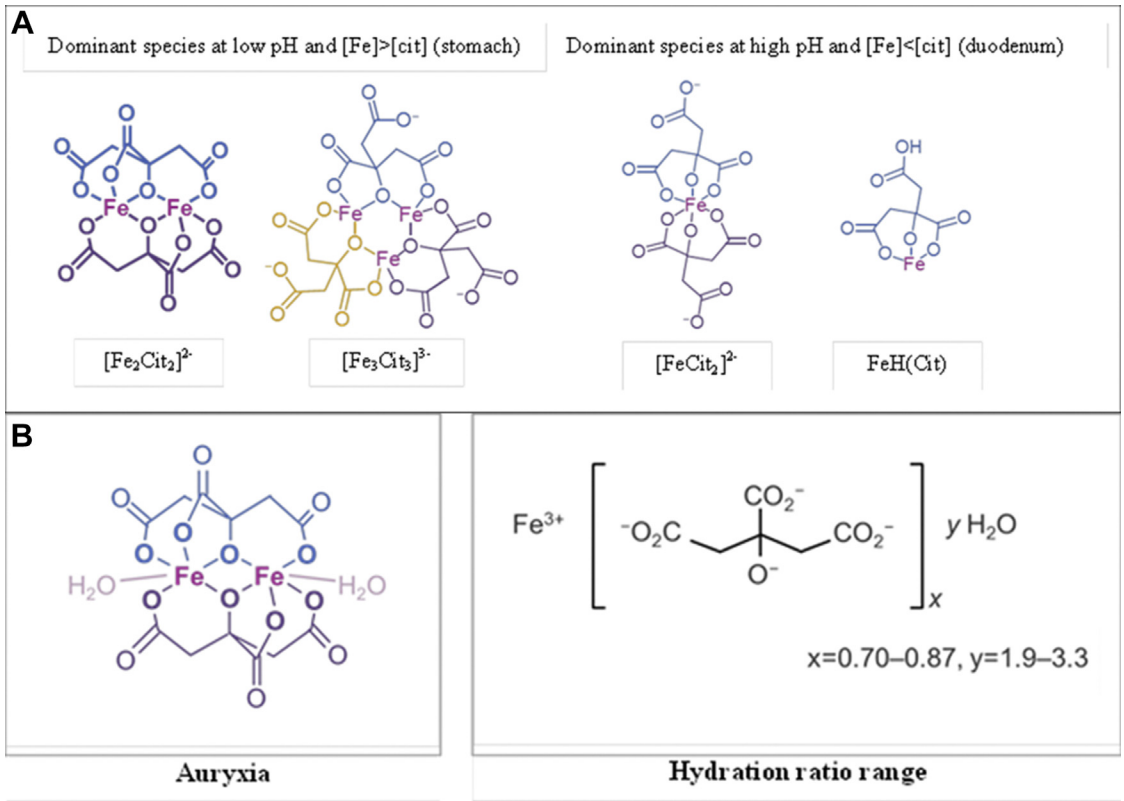

Figure 2. Ferric citrate coordination complexes. (A) Species of FCCCs formed from CGFC; CGFC is a solid mixture of FCCCs, with varying ferric iron citrate molar ratios and hydration. It forms oligomeric complexes at low pH and mononuclear complexes at high pH. (B) FC (Auryxia) coordination complex. Pharmaceutical grade FC has a defined molar ratio of ferric iron to citrate (2:2), a specified range of hydration and is soluble across a broad range of pH. Abbreviations: CGFC, commercial grade ferric citrate; FC, ferric citrate; FCCC, ferric citrate coordination complex. Modified with permission from the Royal Society of Chemistry: *Dalton Trans.*, Silva AM, et al, Iron(III) citrate speciation in aqueous solution, Copyright 2009.[42]

Table 4. Effect of Oral Ferric Citrate on Iron Parameters in Patients With NDD-CKD and DD-CKD

Reference	Study Design/Endpoint	Patient Inclusion Criteria	Dosage and Duration	Changes in Iron Parameters	Changes in Hb	Notes on ESA/IV Iron Usage
Ferric citrate preparations in DD-CKD						
Sinsakul 2012[52]	Phase 2 open-label study of safety and tolerability of FC as a phosphate binder Endpoints: short-term safety, tolerability, and iron absorption	Patients on hemodialysis (3 times a week), serum phosphorus ≥2.5 mg/dL (cohort I) or ≥3.5 mg/dL (cohort II), ferritin <1000 mg/L; TSAT <50% IV iron permitted if ferritin <500 mg/L and TSAT <30% $N = 55$	Cohort I: 4.5 g/d; cohort II: 6 g/d (375 mg capsules of FC) FU at 4 weeks	Mean change (range) in TSAT: 5.35% (–20.5 to 40.5) ($P = 0.001$) Mean change in ferritin: 54.71 ng/mL (–326.5 to 582.5) ($P = 0.02$)	Not reported	45% of patients received IV iron during the treatment period; there was no significant difference in serum iron and TSAT from BL to FU
Yokoyama 2014[53]	Phase 3 open-label dose titration long-term study of FCH as a phosphate binder Endpoints: serum phosphate, calcium, PTH; ferritin, TSAT, doses of ESA and IV iron	Patients on hemodialysis (3 times a week), serum phosphate 3.5-10.0 mg/dL for patients receiving medication for hyperphosphatemia, and 6.1-10.0 mg/dL for patients not on any treatment $N = 180$	1.5 g/d (6 tablets/d); titrated up to 6.0 g/day (24 tablets/d) according to [phosphate] 52-week treatment period FU at 52 weeks	Median (range) TSAT and BL and FU BL: 23.0% (17.8-29.4) FU: 36.35% (28.2-50.05) Median (range) ferritin at BL and FU BL: 57.35 ng/mL (24.75-117.00) FU: 227.00 ng/mL (143.00-342.50)	Mean ± SD Hb at BL and FU BL: 10.97 ± 1.04 FU: 11.15 ± 1.18	Mean weekly ESA dose reduced by 25% from BL (4541 IU/wk) to end-of-treatment (3412 IU/wk) Mean 4 weekly IV iron dose: 57.3 mg (weeks 0-12), 12.8 mg (weeks 12-28), and 3.6 mg (weeks 28-52)
Yokoyama 2014[54]	Phase 3 open-label dose-adjusted study of FCH as a phosphate binder Endpoints: serum phosphate, calcium, PTH; ferritin, TSAT, doses of ESA and IV iron	Patients on peritoneal dialysis for ≥12 weeks who had discontinued phosphate binders with serum phosphate between 5.6 and 10.0 mg/dL $N = 56$	Dose adjusted between 1.5 and 6.0 g of FCH a day according to serum phosphate FCH doses taken after meals	Median (25th, 75th percentile ferritin at BL and FU BL: 85.4 ng/mL (49.0, 128.0) FU: 224.5 ng/mL (173.5, 270.5) $P < 0.001$ Median (25th, 75th percentile) TSAT at BL and FU BL: 32.2% (28.0, 39.2) FU: 47.6% (37.2, 62.0) $P < 0.001$	Mean ± SD Hb at BL and FU BL: 10.67 ± 1.05 g/dL FU: 11.52 ± 1.26 $P < 0.001$	98% of patients used ESAs

(*Continued*)

Table 4. Effect of Oral Ferric Citrate on Iron Parameters in Patients With NDD-CKD and DD-CKD (*Continued*)

Reference	Study Design/Endpoint	Patient Inclusion Criteria	Dosage and Duration	Changes in Iron Parameters	Changes in Hb	Notes on ESA/IV Iron Usage
Lewis 2015[48]	Phase 3 trial of FC as a phosphate binder in patients with ESRD, on hemodialysis or peritoneal dialysis Endpoints: mean change in phosphorus; secondary: ferritin, TSAT, IV iron, ESA usage	Serum ferritin <1000 ng/mL, TSAT <50%, serum phosphorus ≥2.5 and ≤8.0 mg/dL at screening Endpoints: safety and ability to supplement iron stores and reduce ESA and IV iron usage	52-week active control period followed by 4-week open-label placebo control period (at 52 weeks, patients re-randomized to FC or placebo) FC dose adjustments per titration for phosphate levels Active control: calcium acetate, or sevelamer carbonate	Mean ± SD TSAT at BL and FU BL: 31.3% ± 0.7% FU: 39.3% ± 1.1% BL: 30.9% ± 1.0% FU: 29.7% ± 1.0% $P < 0.001$ for FC vs control Mean ± SD ferritin at BL and FU BL: 593 ± 18 ng/mL FU: 899 ± 31 ng/mL BL: 609 ± 26 ng/mL FU: 628 ± 31 ng/mL $P < 0.001$ for FC vs control	At FU, mean ± SD Hb: BL:11.61 ± 0.08 FU:11.42 ± 0.10 BL: 11.71 ± 0.11 FU: 11.14 ± 0.12 ($P = 0.02$ for adjusted mean difference FC vs control)	Yes (82%; 82%) Patients on FC received less IV iron (median = 12.9 mg/wk ferric citrate; 26.8 mg/wk active control; $P < 0.001$) and less ESA (median epoetin-equivalent units/wk: 5303 units/wk FC; 6954 units/wk active control; $P = 0.04$)
Lee 2015[55]	Phase 3 trial of FC in patients with ESRD on maintenance hemodialysis Endpoints: serum phosphorus at week 8 secondary: serum phosphorus at week 4, calcium × phosphorus product at week 4 and week 8, safety was evaluated based on AEs, SAEs, changes in hematological and biochemical laboratory parameters	Patients on maintenance hemodialysis (3 times a week) All patients had serum phosphorus levels of 5.5-10 mg/dL after a 1 to 2-week washout period $N = 75$ (4 g); $N = 72$ (6 g); $N = 36$	4 g (840 mg elemental ferric iron) of FC or 6 g (1260 mg elemental ferric iron) per day of FC or placebo FU 56 days/8 weeks	Median (IQR) change in ferritin from BL to FU 73.90 (3.00-129.60) ng/mL 103.40 (14.00-157.80) ng/mL −41.75 (−131.15 to 13.60) ng/mL Changes against placebo: $P = .008$ for 4 g and .003 for 6 g Median (IQR) change in TSAT from BL to FU 5.35 (−0.50 to 12.20)% 4.95 (−1.80 to 9.90)% −1.15 (−7.00 to 6.65)% Changes not significant vs placebo	Hb from BL to week 8 was not different between the 3 groups 0.30 (−0.50 to 0.70) g/dL 0.60 (−0.10 to 1.30) g/dL 0.35 (−0.40 to 0.65) g/dL ($P = 0.104$) However, as compared to BL, Hb level in the 6 g/d group showed a significant increase at week 4 and week 8 (median 11.1 g/dL at week 4 and 11.3 g/dL at week 8 vs 10.6 g/dL at baseline, $P \leq 0.001$ for both)	Not available

(*Continued*)

Table 4. Effect of Oral Ferric Citrate on Iron Parameters in Patients With NDD-CKD and DD-CKD (*Continued*)

Reference	Study Design/Endpoint	Patient Inclusion Criteria	Dosage and Duration	Changes in Iron Parameters	Changes in Hb	Notes on ESA/IV Iron Usage
Ferric citrate preparations in NDD-CKD						
Yokoyama 2014[56]	Phase 3, double blind, placebo-controlled study of FCH vs placebo in NDD-CKD Endpoints: serum phosphate, calcium, calcium × phosphate product, total iron, ferritin, TIBC, TSAT, safety	Serum phosphate ≥5.0 and <8.0 mg/dL during screening period $N = 57$; $N = 29$	1.5 g/day FCH after a meal vs placebo for 12 weeks Dose adjustment per phosphate levels Follow-up at 12 weeks	Mean ± SD TSAT at BL and FU BL: 27.22 ± 11.30% FU: 44.19 ± 20.88% BL: 24.99 ± 12.75% FU: 27.03 ± 12.60% $P < 0.001$ for FC vs control Mean ± SD ferritin at BL and FU BL: 69.00 ± 50.92 ng/mL FU: 204.01 ± 106.54 ng/mL BL: 105.98 ± 95.58/mL FU: 93.66 ± 82.70 ng/mL $P < 0.001$ for FC vs control	Although there was no significant difference between groups, Hb increased from 10.3 to 10.7 g/dL ($P = 0.04$) in the FCH group	ESA: N/A IV iron usage was permitted
Block 2015[57]	Phase 2 randomized study of FC vs placebo in patients with non-dialysis-dependent CKD Endpoints: change in TSAT and serum phosphate from BL to end of study Secondary: change from BL in ferritin, hemoglobin, iFGF23, urinary phosphate, eGFR	eGFR <60 mL/min/1.73 m^2, iron deficiency anemia (Hb between 9.0 and 12.0 g/dL; TSAT ≤30%, serum ferritin ≤300 ng/mL), serum phosphate ≥4.0 to 6.0 mg/dL $N = 72$; $N = 69$	FC initiated at a dose of 3 × 210 mg/d elemental iron given after meals, dose adjusted based on serum phosphate Treatment for 12 weeks	Mean change (±SD) in TSAT from BL to FU BL: 22% ± 7% FU: 32% ± 14% BL: 21% ± 8% FU: 20% ± 8% Treatment effect difference for TSAT: 11.3% [95% CI 8.0-14.7] Mean change (±SD) in ferritin from baseline to follow-up BL: 116 ± 83 ng/mL FU: 189 ± 122 ng/mL BL: 110 ± 81 ng/mL FU: 106 ± 94 ng/mL	Mean change in Hb BL: 10.5 ± 0.8 g/dL FU: 11.0 ± 1.0 g/dL; BL: 10.6 ± 1.1 g/dL FU: 10.4 ± 1.1 g/dL Treatment effect difference: 0.6 (95% CI 0.4-0.9), $P < 0.001$ vs placebo	No ESAs within 4 weeks or IV iron within 8 weeks

(*Continued*)

Table 4. Effect of Oral Ferric Citrate on Iron Parameters in Patients With NDD-CKD and DD-CKD (*Continued*)

Reference	Study Design/Endpoint	Patient Inclusion Criteria	Dosage and Duration	Changes in Iron Parameters	Changes in Hb	Notes on ESA/IV Iron Usage
Fishbane 2017[51]	Phase 3 randomized study of FC vs placebo in patients with non-dialysis-dependent CKD and IDA Endpoint: proportion of patients who achieved ≥1.0 g/dL increase in Hb at any time during a 16-week randomized period	eGFR <60 mL/min/1.73 m^2 and iron deficiency anemia (Hb between 9.0 and 11.5 g/dL inclusive, ferritin ≤200 ng/mL, TSAT ≤25%) Intolerant of, or with inadequate response to oral iron, and serum phosphate ≥3.5 mg/dL $N = 117$; $N = 116$	16 weeks (and 8-week open-label extension period) FC initiated at a dose of 3 × 210 mg/d elemental iron given after meals, dose was titrated at weeks 4, 8, and 12 aiming to achieve an increase in Hb by >1.0 g/dL above BL	Mean relative changes (FC vs placebo) in TSAT at week 16: 18.4% (95% CI 14.6-22.2; $P < 0.001$) Mean relative changes (FC vs placebo) in ferritin at week 16: 170.3 ng/mL (95% CI 144.9-195.7 ng/mL; $P < 0.001$)	Mean relative change in Hb (FC vs placebo) at week 16: 0.84 g/dL (95% CI 0.58-1.10 g/dL) ($P < 0.001$) Patients randomized to FC were significantly more likely to achieve the primary endpoint (≥1 g/dL increase in Hb) 61 of 117 [52.1%] vs 22 of 115 [19.1%]; $P < 0.001$	Patients with ESA or IV iron use within 4 weeks of screening were excluded

Abbreviations: AE, adverse event; BL, baseline; CI, confidence interval; CKD, chronic kidney disease; DD-CKD, dialysis-dependent CKD; eGFR, estimated glomerular filtration rate; ESA, erythrocyte-stimulating agent; ESRD, end-stage renal disease; FC, ferric citrate; FCH, ferric citrate hydrate; FU, follow-up; Hb, hemoglobin; IDA, iron deficiency anemia; iFGF23, intact fibroblast growth factor 23; IQR, interquartile range; IV, intravenous; N/A, not applicable; NDD-CKD, non-dialysis-dependent CKD; PTH, parathyroid hormone; SAE, serious adverse event; SD, standard deviation; TIBC, total iron binding capacity; TSAT, transferrin saturation.

agent in patients with NDD-CKD and IDA; FC significantly improved iron parameters and Hb levels vs placebo,[51] which led to its approval as an iron repletion agent in 2017 for the treatment of IDA in adult patients with NDD-CKD.[49]

Clinical Studies With Ferric Citrate—Efficacy Data for Iron Repletion. Following a favorable initial phase 2 open-label study in patients with DD-CKD ($n = 55$; Table 4),[52] a 52-week phase 3 trial ($n = 441$) evaluated the efficacy of FC as a phosphate binder ($n = 292$) vs active control ($n = 149$). Secondary outcomes were changes in ferritin and TSAT and cumulative IV iron and ESA doses. At baseline, mean serum ferritin levels were 594 ng/mL (FC) and 595 ng/mL (control), and mean TSAT 30.9% (FC) and 30.8% (control).[48,50] FC was administered with meals (1-g tablets; 210 mg elemental iron each) and dose adjustments were made based on serum phosphorus values rather than Hb. The median daily FC dose was 8.0 tablets/d (1680 mg elemental iron). Compared with control, FC significantly increased ferritin (mean treatment difference: 114.1 ± 29.35 ng/mL; $P < 0.001$) and TSAT (mean treatment difference: 8.62% ± 1.57%; $P < 0.001$) by week 12, and these differences were maintained or increased at week 52 (mean treatment differences: 281.8 ± 42.9 ng/mL and 9.55% ± 1.58% for ferritin and TSAT, respectively; $P < 0.001$).[48,50] At week 52, mean Hb levels were significantly higher with FC vs active control (Table 4).[45] Patients receiving FC required less cumulative elemental IV iron and had lower cumulative ESA use at 52 weeks.

In a 12-week double-blind placebo-controlled phase 2 trial of FC in 149 patients with NDD-CKD and IDA (CKD stage 3-5, Hb 9.0-12.0 g/dL, TSAT ≤30%, and serum ferritin ≤300 ng/mL; FC, $n = 75$; placebo, $n = 74$), coprimary endpoints were changes in TSAT and serum phosphate levels (Table 4).[57] The initial dose of FC was 3 tablets a day (630 mg elemental iron) with meals, and adjusted based on serum phosphate levels; the mean daily FC dose was 5.1 g/d (1050 mg elemental iron). After 12 weeks of treatment, FC significantly increased mean Hb levels (10.5 ± 0.8 to 11.0 ± 1.0 g/dL; $P < 0.001$ vs placebo), mean TSAT levels (22% ± 7% to 32% ± 14%; $P < 0.001$ vs placebo), and mean ferritin levels (116 ± 83 to 189 ± 122 ng/mL; $P < 0.001$ vs placebo) (Table 4).[57]

Focusing on IDA, a phase 3 randomized, placebo-controlled clinical trial of FC was done in patients with NDD-CKD who had an inadequate response to, or were intolerant of, prior oral supplementation (FC, $n = 117$; placebo, $n = 116$).[58] At baseline, mean ferritin levels were 85.9 ng/mL (FC) and 82.2 ng/mL (placebo) and mean TSAT 20.2% (FC) and 19.5% (placebo). FC was initiated at 3 tablets daily (with meals) and titrated at weeks 4, 8, and 12 by additional 3 tablets/d to achieve an Hb increase of >1.0 g/dL above baseline; the mean daily dose of FC was 5.0 tablets (1050 mg elemental iron). A significantly higher proportion of patients who received FC vs

placebo (52.1% vs 19.1%) achieved the primary endpoint of ≥1.0 g/dL increase in Hb at any time from baseline to the end of the 16-week randomized period. Significant increases in ferritin concentrations and TSAT were noted in FC-treated patients compared with placebo (Table 4). Based on the results of this trial, FC was approved as an iron-repletion agent in NDD-CKD.[49]

A subsequent post hoc analysis showed that patients with lower baseline TSAT and ferritin (ie, those with more pronounced iron deficiency) experienced greater increases in Hb after 16 weeks of treatment.[59] In addition, lower baseline levels of iFGF23 and higher serum albumin levels at baseline were associated with a greater Hb increase, suggesting that the Hb response to iron in patients with CKD is likely dependent on the severity of inflammation and IDA.[59] Another post hoc analysis of the phase 3 study showed that the efficacy of FC was similar in patients with NDD-CKD and IDA with or without concomitant heart failure.[60]

Although the above-mentioned studies examined FC (Auryxia), other FC preparations such as FC (Nephoxil; 105 mg elemental iron per tablet; Table 1) or ferric citrate hydrate (FCH; Riona; 45 mg elemental iron per tablet; Table 1) have also shown effectiveness in improving Hb and iron parameters in patients with CKD, although these studies evaluated FC as a phosphate binder and not as an oral iron supplement. Results of these studies are summarized in Table 4.

Effect on Ferric Citrate Treatment on the Use of ESAs and IV Iron. Perhaps the most encouraging results from FC use, particularly in DD-CKD, have been the substantial reductions in the use of ESAs and IV iron in FC-treated patients (Table 4). In the phase 3 trial that evaluated FC vs active control in patients with DD-CKD,[48,50,61] FC-treated patients required less cumulative elemental IV iron than those receiving active control over the 52-week randomized period (median dose 12.9 vs 26.88 mg/week; $P < 0.001$). At week 52, 85% of patients in the FC group received no IV iron compared with 69% in the active control group. Similarly, the cumulative ESA use was lower in FC-treated patients over the 52-week period (median dose 5303 vs 6954 U/wk for active control; $P = 0.04$).

Similarly, a large open-label trial of FCH (Riona) in patients with CKD on hemodialysis showed a 25% reduction in the mean weekly ESA dose over a 52-week treatment period (from 4541 IU/wk at baseline to 3412 IU/wk at week 52).[53] In addition, the mean IV iron dose (per 4 weeks) declined from 57.3 mg in weeks 0 to 12 to 3.6 mg in weeks 28 to 52.[53] An ongoing trial (NCT02492620) is currently evaluating the impact of administering a fixed dosage of FC (vs standard of care) on ESA usage, IV iron usage, and time to dialysis in patients with late-stage NDD-CKD.[62] Preliminary results from this trial indicated that FC treatment significantly improved iron parameters and Hb levels, and reduced ESA and IV iron dosages administered vs standard of care. In addition, results suggested benefit on time to death or dialysis in FC-treated patients.[62] Another study (NCT02888171) is also underway to compare the effect of FC (1260 mg/d elemental iron) vs ferrous sulfate (200 mg/d elemental iron) on iron parameters (serum iron, TSAT, ferritin, hepcidin) and Hb in patients with moderate-to-severe CKD and absolute iron deficiency. Currently, there is a lack of long-term data on iron therapy with FC, thus the COMPASS trial (a phase 4 study of KRX-0502 [ferric citrate] dose regimens in subjects with non-dialysis-dependent CKD and iron deficiency anemia) (NCT03236246) is investigating the long-term efficacy and safety (48 weeks) of different dose regimens of FC in patients with IDA and NDD-CKD.

Another important question is whether FC impacts the use of ESAs in patients with NDD-CKD either by delaying the need to start them or by decreasing their maintenance dose when used concomitantly. To date, most randomized trials of FC in this patient population excluded the use of ESAs; therefore, no studies have examined the potential ESA-sparing effect of FC use. In theory, it would be ideal to initiate FC in patients with NDD-CKD as soon as IDA is diagnosed (TSAT <30%, ferritin <300 ng/mL), which would likely reduce the need for transfusions, ESAs, and IV iron use. Also, if anemia can be corrected without using ESA at least in some patients (as suggested by the available data for those with lower TSAT, ferritin, and fibroblast growth factor 23 (FGF23) and higher serum albumin levels at baseline), maintaining Hb within normal levels may be a safe goal to achieve.

FC was shown to reduce FGF23 levels in patients with NDD-CKD and IDA,[51,57] and elevated FGF23 levels have been independently correlated with cardiovascular mortality in CKD.[63] Therefore, it will be of interest to determine whether FC has an impact on long-term cardiovascular outcomes in this patient population. Over the next 5 years, it will be also informative to explore the use of FC for the treatment of anemia in other conditions, such as ulcerative colitis, pregnancy, heart failure, and cancer, since safety concerns have been raised regarding the use of ESA therapy in cancer-related anemia; these patients could potentially benefit from the use of an efficacious oral supplementation, like FC.[64]

Safety of Ferric Citrate. Studies of FC in DD-CKD and NDD-CKD demonstrated low overall rates of SAEs and treatment-related discontinuations with FC in both patient populations (Table 5). In a study of 441 patients with DD-CKD,[48] patients receiving FC (Auryxia) experienced similar rates of treatment-emergent AEs (90.3% vs 89.3%) and a lower incidence of SAEs (39.1% vs 49.0%) than patients receiving active control. The most common SAEs were GI-related (6.9% with FC vs 12.8% with active control), infection-related (12.5% vs 18.1%), and cardiac-related (7.3% vs 12.1%). Most noncomparative studies of FC or FCH in DD-CKD showed GI AEs as the most frequent AEs reported.[52-54] In one study of FCH in patients with CKD on hemodialysis, the incidence of infectious and parasitic disease (in 71% of FCH-treated patients) was higher than GI-related events, but most of these events were not considered related to FCH treatment.[53]

Table 5. Ferric Citrate—Safety

Reference	Study Design	Patient Population	FC Dosage and Duration	Incidence of AEs in FC-Treated Patients Overall, Serious	Most Common AEs in ≥5% of FC-Treated Patients (Incidence in %)	Discontinuations due to AEs in FC-Treated Patients, n (%)
Ferric citrate preparations in DD-CKD						
Sinsakul 2012[52]	Phase 2 open-label study of safety and tolerability of FC as a phosphate binder	Patients on maintenance hemodialysis, (3 times a week) *N* = 55	Cohort I: 4.5 g/d; cohort II: 6 g/d (375 mg capsules of FC) Follow-up at 4 weeks	TEAEs: Overall: not reported Serious: 4 (7%)—liver infection, bacteremia, suicide attempt, and congestive heart failure	TEAEs: change in stool color (62%); constipation (15%); bloating (7%); diarrhea (7%); nausea (5%); stomach pain (5%)	TEAEs: 6 (11%) constipation (7%), bloating (4%), diarrhea (4%)
Yokoyama 2014[53]	Phase 3 open-label dose titration long-term study of FCH as a phosphate binder	Patients on maintenance hemodialysis (3 times a week) *N* = 180	1.5 g/d (6 tablets/d); titrated up to 6.0 g/d (24 tablets per day) according to [phosphate] 52-week treatment period	ADR (drug-related): Overall: 49 (27%) Serious: 2 (0.6%)—both unrelated to drug (pneumonia, putaminal hemorrhage)	ADR (drug-related): gastrointestinal disorders (19%); diarrhea (12%)	ADR (drug-related): 8 (4%) elevated hemoglobin (2%), diarrhea (1%), elevated ferritin, liver dysfunction, elevated serum aluminum
Yokoyama 2014[54]	Phase 3 open-label dose-adjusted study of FCH as a phosphate binder	Patients on peritoneal dialysis for ≥12 weeks *N* = 56	Dose adjusted between 1.5 and 6.0 g of FCH per day according to serum phosphate FCH doses taken after meals	ADR (drug-related): Overall: 21 (38%) Serious: 1 (2%) Abnormal hepatic function	ADR: diarrhea (7%); constipation (7%); nausea (5%); vomiting (5%); frequent bowel movements (5%)	ADR: 1 (2%) cardiac failure (not drug-related)
Lewis 2015[48]	Phase 3 trial of FC as a phosphate binder in DD-CKD (hemodialysis or peritoneal dialysis)	DD-CKD, hemodialysis or peritoneal dialysis usage *N* = 292 *N* = 149	52-week active control period followed by 4-week open-label placebo control period (at 52 weeks, patients re-randomized to FC or placebo) FC dose adjustments per titration for phosphate levels Active control: calcium acetate or sevelamer carbonate	TEAEs: Overall: 261 (90.3%) vs 261 (89.3%) Serious: 113 (39.1%) vs 113 (49.0%)	TEAEs: GI serious AEs: 6.9% vs 12.8% Infection serious AEs: 12.5% vs 18.1% Cardiac serious AEs: 7% vs 12.1%	Not reported
Lee 2015[55]	Phase 3 trial of FC in DD-CKD (maintenance hemodialysis)	Patients on maintenance hemodialysis (3 times a week) *N* = 36 *N* = 75 (4 g) *N* = 72 (6 g)	4 g (840 mg elemental ferric iron) or 6 g (1260 mg elemental ferric iron)/day of FC or placebo Follow-up 56 days	Overall AE incidence not reported In the 4 g/d group, 1 (1%) experienced serious AEs (not related) In the 6 g/d group, 4 (6%) experienced serious AEs (not related)	Most common treatment-related AEs in 4 g/d group: discolored feces (37.3%); diarrhea (6.7%) In 6 g/d group: discolored feces (37.5%) In placebo: discolored feces (5.6%); diarrhea (5.6%)	Discontinuations because of AEs: 2 (3%) in 4 g/d group 7 (10%) in the 6 g/d group

(*Continued*)

Table 5. Ferric Citrate—Safety (*Continued*)

Reference	Study Design	Patient Population	FC Dosage and Duration	Incidence of AEs in FC-Treated Patients Overall, Serious	Most Common AEs in ≥5% of FC-Treated Patients (Incidence in %)	Discontinuations due to AEs in FC-Treated Patients, n (%)
Ferric citrate preparations in NDD-CKD						
Yokoyama 2014[56]	Phase 3, double-blind, placebo-controlled study of FCH vs placebo in NDD-CKD	Serum phosphate ≥5.0 and <8.0 mg/dL during screening period $N = 60$; $N = 30$	1.5 g/d FCH after a meal vs placebo for 12 weeks Dose adjustment per phosphate levels Follow-up at 12 weeks	Overall AEs: 41 (68.3%) vs 18 (60.0%) Overall serious AEs: 8 (13.3%) vs 3 (10%) ADR (drug-related): 19 (32%) vs 8 (26.7%)	Most common adverse drug reactions: diarrhea (13%), constipation (12%), abdominal discomfort (5%), abdominal distension (5%)	Discontinuations due to AEs: 5 (8%) vs 1 (3%)
Block 2015[57]	Phase 2 randomized study of FC vs placebo in patients with NDD-CKD	Patients with NDD-CKD and IDA (Hb between 9.0 and 12.0 g/dL; TSAT ≤30%, serum ferritin ≤300 ng/mL), serum phosphate ≥4.0-6.0 mg/dL $N = 72$; $N = 69$	FC initiated at a dose of 3 × 210 mg/d elemental iron given after meals, dose adjusted based on serum phosphate Treatment for 12 weeks	Overall TEAEs: 52 (69.3%) vs 43 (58.9%) Overall serious TEAEs: 8% vs 12% (none related to treatment)	Most common TEAEs: discolored feces (32%); diarrhea (20%); constipation (6.7%); vomiting (5%); upper respiratory tract infections (5%) nausea (7%)	Discontinuations due to AEs: 13% vs 11%
Fishbane 2017[51]	Phase 3 randomized study of FC vs placebo in patients with NDD-CKD and IDA	Patients with NDD-CKD and IDA $N = 117$; $N = 116$	16 weeks (and 8-week open-label extension period) FC initiated at a dose of 3 × 210 mg/d elemental iron given after meals, dose was titrated at weeks 4, 8, and 12 aiming to achieve an increase in Hb by >1.0 g/dL above BL	Overall TEAEs: 93 (79.5%) vs 75 (64.7%) Drug-related TEAEs: 35 (29.9%) vs 26 (22.4%) Overall serious AEs (not related to treatment): 14 (12%) vs 13 (11.2%)	Most common TEAEs: diarrhea (21%); constipation (19%); discolored feces (15%); nausea (11%); abdominal pain (6%); hyperkalemia (7%)	Not reported

Abbreviations: ADR, adverse drug reaction; AE, adverse event; BL, baseline; CKD, chronic kidney disease; DD-CKD, dialysis-dependent CKD; ESRD, end-stage renal disease; FC, ferric citrate; FCH, ferric citrate hydrate; GI, gastrointestinal; Hb, hemoglobin; IDA, iron deficiency anemia; IV, intravenous; NDD-CKD, non-dialysis-dependent CKD; TSAT, transferrin saturation; TEAE, treatment emergent adverse events.

A pooled analysis of 2 randomized controlled trials of FC (Auryxia) in NDD-CKD[51,57] showed that the most common treatment-emergent events with FC were GI-related and included discolored feces (a known side effect of iron salts), diarrhea, constipation, and nausea.[65] The incidence of all GI AEs declined over time despite an increase in the study medication dose.[65] SAEs were not common with FC, and rates were similar to placebo (10.5% vs 11.2%); the most common SAEs were cardiac disorders (FC vs placebo: 3.7% vs 2.7%) and infections/infestations (2.6% vs 3.7%); none were considered to be treatment-related.[65] Among FC-treated patients, 10 (5.3%) discontinued due to GI-related AEs (vs 2 [1.1%] in the placebo group).

Of note, the incidence of hypophosphatemia was low with FC in NDD-CKD: <1% of patients had suspected drug-related hypophosphatemia in the phase 3 trial,[51] and no episodes of symptomatic hypophosphatemia were noted in the phase 2 trial.[57] Unlike with certain IV iron preparations,[41] the incidence of hypophosphatemia is low with FC, suggesting that routine monitoring of serum phosphorus levels may not be required unless the starting serum phosphorus is low (<2.5 mg/dL). As all studies to date have administered FC with meals, it is recommended that FC be always taken with meals.

GI-related AEs with oral iron often have a high correlation with the elemental iron dosage.[23] For reference, in a systematic meta-analysis of conventional oral iron agents (not including FC), whose daily elemental iron dose did not exceed 200 mg, the incidence of GI AEs in patients with CKD ranged from 4% to 63%.[66] No studies have directly compared FC with conventional oral agents, and a comparison across trials is difficult, given the differences in endpoints and AE-reporting methods. Yet, it may be noted that the incidence of GI-related AEs with FC is unremarkable, considering that >1000 mg daily elemental iron was administered in these patients. Although no data specific to FC are available, the likely explanation is that the ferric form of iron is much less soluble and less reactive with mucosal surfaces than the ferrous form, and that the conversion of the ferric to the absorbable ferrous form occurs under locally controlled conditions (eg, the presence of ferric reductases like duodenal cytochrome b).

Ferric Maltol

Chemical Properties and Preclinical Studies. Ferric maltol is a novel oral iron therapy consisting of a stable complex of ferric (Fe3+) iron with maltol (3-hydroxy-2-methyl-4-pyrone), which is a naturally occurring sugar derivative formed during caramelization.[67] The ferric trimaltol complex is formed at a 3:1 iron:maltol ratio, which prevents the formation of iron hydroxide polymers, allowing bioavailable iron at the neutral pH of the intestinal tract.[67] Ferric trimaltol has both hydrophilic and lipophilic properties and, following oral administration, ferric iron reaches the intestinal mucosa in complex form, which may allow for more efficient uptake of elemental ferric iron into the enterocytes vs ferrous iron salts.[68-70] This high bioavailability may allow for administration of lower daily iron doses.[67] In addition, resistance to lipid peroxidation conferred by the maltol entity protects against tissue damage and improves the safety profile.[71]

Approvals and Indications. Ferric maltol (Feraccru/Accrufer; Shield Therapeutics, Inc.) is approved in the European Union and the United States for the treatment of IDA in adults and in Switzerland for the treatment of IDA in patients with inflammatory bowel disease. The new drug application for ferric maltol was filed with the US FDA in October 2018 for the treatment of IDA in patients with inflammatory bowel disease.[72] Ferric maltol also was evaluated in a phase 3 trial in adults with IDA and NDD-CKD (discussed below) and in a phase 1 trial in pediatric patients with iron deficiency (NCT03181451).

Clinical Studies. Ferric maltol was evaluated in a 12-week open-label, uncontrolled proof-of-concept study to determine the tolerability and efficacy in patients with IDA with documented intolerance to ferrous sulfate ($n = 23$; including 15 patients with inflammatory bowel disease).[73] At 12 weeks, ferric maltol increased mean Hb from 10.6 ± 1.5 g/dL at baseline to 12.6 ± 1.6 g/dL ($P < 0.001$, paired t-test). In addition, ferric maltol increased mean ferritin levels from 8.1 ± 3.5 μg/L at baseline to 17.4 ± 11.4 μg/L at 12 weeks ($P < 0.001$). No SAEs were observed.

Ferric maltol was evaluated in a pivotal, randomized, double-blind, placebo-controlled phase 3 trial in patients with IDA and NDD-CKD ($N = 168$; AEGIS-CKD study; NCT02968368). The trial consisted of a 16-week double-blind treatment phase in which patients were randomized to receive either ferric maltol 30 mg orally twice daily or placebo, followed by a 36-week open-label extension phase in which all patients received ferric maltol. Ferric maltol was superior to placebo in increasing Hb at 16 weeks (0.5 ± 0.122 vs −0.02 ± 0.165 g/dL; $P = 0.0149$); improvements in patients initially randomized to ferric maltol were maintained during the 36-week open-label extension period.[74] Patients initially randomized to placebo who initiated ferric maltol at week 16 demonstrated an Hb increase similar to patients initially randomized to ferric maltol during their first 16 weeks of treatment. Ferric maltol was well tolerated, and 74% of patients entering the open-label extension phase completed the 52-week study.

Sucrosomial Iron Chemical Properties

Sucrosomial iron is an oral iron preparation consisting of ferric pyrophosphate protected by a phospholipid bilayer membrane.[75] The phospholipid layer is made primarily of a sunflower lecithin and sucrester matrix.[76] Sucrester is a surfactant created by esterification of fatty acids with sucrose (sucrose esters). Other ingredients such as tricalcium phosphate and starch are used to coat the molecule, which forms the "sucrosome."

Preclinical Data. Preclinical data have shown that sucrosomial iron retains the iron in the sucrosome when in stomach acid, which allows intact sucrosomes to reach the small

intestine where they are absorbed.[77] The presence of sucrester protects the ferric ions from reduction by intestinal enzymes, and promotes ferric ion transport across the intestinal epithelium independent of the divalent metal transporter 1 carrier. In addition, sucrosomial iron showed increased intestinal absorption, as vesicle-like structures, and enhanced bioavailability vs ferric pyrophosphate in animal studies.[78] Absorption of sucrosomial iron has been shown to occur through the microfold cells of the Peyer's patches in the small intestine (M cells) where it is taken up by macrophages into the lymphatic circulation.[76,78]

In Caco-2 cell cultures, sucrosomial iron resulted in a 3-fold increase in ferritin accumulation vs ferrous sulfate.[79] Cell culture data also indicated that sucrosomial iron increased ferritin expression in enterocytes in vitro. In iron-deficient piglets, sucrosomial iron improved all red blood cell indices, with similar effects on iron parameters compared with iron dextran; however, no excess iron accumulation was observed in the liver, spleen, brain, heart, or kidneys, and hepatic hepcidin messenger RNA levels were not elevated.[80] In addition, sucrosomial iron improved Hb levels and iron status in a study of anemic mice, with no significant increase in hepcidin expression.[81]

Clinical Evaluation in Chronic Kidney Disease. A randomized open-label trial evaluated oral sucrosomial iron in NDD-CKD patients (N = 99) with IDA (defined as Hb ≤12 g/dL, ferritin ≤ 100 ng/mL, TSAT ≤25%).[32] Patients were randomized 2:1 to receive oral sucrosomial iron 30 mg/d for 3 months or IV ferrous gluconate 125 mg/wk to a total dose of 1000 mg, with follow-up of 4 months. Mean Hb levels were similar in the sucrosomial iron and IV ferrous gluconate groups (11.4 vs 11.7 g/dL, respectively). The proportion of patients who achieved at least a 0.6 g/dL increase in Hb at any point between baseline and end of treatment was significantly greater with IV ferrous gluconate vs oral sucrosomial iron (33.3% vs 8.7% at 1 month, 52.2% vs 27.3% at 2 months, and 56.2% vs 43.5% at 3 months, $P < 0.05$). Mean increases in ferritin were significantly greater in the IV ferrous gluconate group (238.5 ng/mL) than in the oral sucrosomial iron group (85.5 ng/mL; $P < 0.05$). Hb concentrations decreased to pretreatment values in the month after treatment discontinuation in the oral sucrosomial iron group, whereas Hb concentrations remained stable after discontinuation of IV ferrous gluconate, suggesting that less iron enters stores from the sucrosomial form. Significantly fewer AEs considered at least possibly related to treatment were observed in the oral sucrosomial iron group compared with the IV ferrous gluconate group (3.1% vs 34.5%; $P < 0.001$). The most common AEs were headache (18%), hypotension (12%), and infusion site reaction (12%) in the IV ferrous gluconate group and constipation (5%) and diarrhea (5%) in the sucrosomial iron group; no SAEs were observed in either treatment group. Treatment adherence was similar in the 2 groups. This study indicates that short-term oral sucrosomial iron was as effective as IV ferrous gluconate at correcting anemia in NDD-CKD patients, with a favorable tolerability profile. Sucrosomial iron also has been evaluated in several other clinical settings, including IDA associated with pregnancy, inflammatory bowel disease, celiac disease, cancer, and bleeding.[76,82-85]

CONCLUSIONS

Anemia is a common and undertreated comorbidity in CKD. As conventional oral irons have generally not been highly effective or well tolerated in this patient population, current treatments tend to rely on ESAs and IV irons, which are associated with the risk of SAEs, including cardiovascular events. FC is an oral iron repletion agent approved to treat IDA in the NDD-CKD patient population; it has a favorable safety and efficacy profile and may spare IV iron and ESA use, and possibly delay the transition to dialysis. FC improved iron parameters and reduced ESA and IV iron exposure in patients with DD-CKD; however, its role as an iron-repletion agent in this patient population remains to be clarified. Other novel oral iron preparations also are in development for IDA in patients with CKD. Ferric maltol demonstrated improvements in Hb vs placebo with a favorable tolerability profile in a pivotal phase 3 trial in patients with NDD-CKD. Sucrosomial iron, which has been evaluated in IDA associated with CKD and several other clinical settings, demonstrated improved tolerability over IV iron.

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