Recent and Emerging Therapies for Iron Deficiency in Anemia of CKD: A Review

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Abstract:

Iron deficiency commonly contributes to the anemia affecting individuals with chronic kidney disease. Diagnostic criteria for iron deficiency in chronic kidney disease are explained. Mechanisms of functional and absolute iron deficiency and general treatment principles as delineated in the Kidney Disease: Improving Global Outcomes guidelines are reviewed. Repletion of absolute iron deficits has progressed over time with the addition of better tolerated, more effective oral agents including ferric citrate, ferric maltol, and sucrosomial iron. Structural characteristics and trial data enabling regulatory approval of these novel oral agents are examined. Newer intravenous iron therapies including ferric carboxymaltose and ferric derisomaltose allow for fewer infusions and decreased risk of serious hypersensitivity reactions. Concerns about adverse events including cardiovascular events and infections are discussed. The potential risk of 6H syndrome due to these intravenous agents, including hypophosphatemia, osteomalacia, and pathologic fractures is emphasized. The proposed pathophysiology of 6H syndrome and hypophosphatemia is described. Ferric pyrophosphate citrate enables administration of iron for repletion through dialysate. Relative merits, costs, and risks of various iron agents such as hypersensitivity and 6H syndrome/hypophosphatemia are summarized.

Key Words: iron, chronic kidney disease, anemia, hemoglobin, 6H syndrome
Introduction

Pathophysiology of Iron Deficiency Anemia

Normal iron homeostasis depends on adequate absorption of iron from the diet. Absorbed iron replaces losses due to menstruation and sloughing of epithelial cells from the skin and intestines.\(^1\) Iron in the body is tightly regulated because there are no natural mechanisms for its excretion. The mechanisms of iron absorption and internal distribution are summarized in Figure 1.

Functional vs. Absolute Iron Deficiency

In patients with chronic kidney disease (CKD), the unavailability of iron for hematopoiesis can be absolute or functional. Absolute iron deficiency occurs when the amount of storage iron in the liver, spleen, and marrow is minimal. This may stem from blood losses related to the dialysis procedure, gastrointestinal bleeding, or poor oral iron intake.\(^2\) It has been estimated that the prevalence of iron deficiency anemia in the US has increased from 10.5% to 106% between 1999 and 2018 depending upon age and sex. This has been attributed to a cultural dietary shift from beef to poultry-based food products over that time period.\(^3\) Functional iron deficiency is characterized by adequate iron stores, the gold standard for which is presence of stainable iron in bone marrow, but usually diagnosed in the clinical setting by blood tests as noted below.\(^4\) Functional iron deficiency represents a supply-demand mismatch for iron to support erythropoiesis. On the supply side, inflammation leads to decreased iron availability primarily due to elevated hepcidin concentration in plasma. On the demand side, erythropoiesis stimulating agents (ESAs) used in CKD patients accelerate red blood cell production and exceed the ability to sufficiently mobilize iron from stores. Functional iron deficiency due to ESA therapy can
often be overcome with therapeutic iron supplementation, whereas anemia of inflammation may be more resistant to this intervention (Box 1). 7

**Diagnosis of Iron Deficiency Anemia**

Absolute iron deficiency in CKD patients is defined when transferrin saturation (TSAT) is <20% and ferritin <100 ng/mL. Functional iron deficiency is defined by TSAT <20% and ferritin >100 ng/mL in CKD without kidney replacement therapy (KRT) and >200 ng/mL in dialysis dependent CKD (DD-CKD). However, these parameters have been questioned and are an area of active review. 8 Since inflammation, which is highly prevalent in CKD, can raise ferritin and lower transferrin concentration in plasma, this compromises the applicability of these standard diagnostic tests. Alternative measures such as reticulocyte hemoglobin content and percentage of hypochromic RBCs have been proposed. However, limited availability of these assays has restricted their use in clinical practice, particularly in the US. 9

**Principles of Management**

The 2012 KDIGO Guidelines on Anemia Management in CKD suggest treating anemia with iron supplementation in adult CKD stage 3-5 patients when TSAT is <30% and ferritin is <500 ng/mL. The goal is to balance transfusion avoidance with the risks and side effects of iron therapy. 10 The evidence base for these recommendations in adults is not robust. In pediatric patients with anemia not already receiving therapy, treating TSAT <20% and ferritin <100 ng/mL with iron is recommended in all CKD 3-5 patients. The evidence base for this recommendation is stronger than that in adults, but noting that estimates of response are less likely to be accurate, it is presented as an opinion that intravenous (IV) iron be avoided during active infection. 10
A Cochrane Review of 28 studies with 2098 participants comparing oral vs. IV iron therapy for patients with CKD\textsuperscript{11} provided strong evidence for increased ferritin (mean difference [MD] 243.25 ng/mL, 95% CI 188.74 to 297.5) and TSAT (MD 10.20%, 95% CI 5.56 to 14.83) among patients treated with IV iron. The difference in hemoglobin (Hb) increase among patients treated with IV iron was also significant (MD 0.90 g/dL, CI 0.44 to 1.37). Morbidity and cardiovascular mortality did not differ significantly between the two groups, but were reported in few studies.

An updated meta-analysis in 2016\textsuperscript{12} showed that patients with stages 3-5 CKD including stage 5D treated with IV iron were more likely to achieve a Hb increase $>1$g/dL (R 1.61, 95% CI 1.39-1.87) than those treated with oral iron. Safety analysis showed similar rates of mortality and adverse events, although IV iron was associated with a higher risk of hypotension (RR 3.71, 95% CI 1.74-7.94) and lower risk of gastrointestinal adverse events (RR 0.43, 95% CI 0.28-0.67).

The authors recommended increased use of IV iron for patients with CKD stages 3-5.\textsuperscript{12} The KDIGO guidelines agree that IV iron is generally more effective than oral iron for hemodialysis (HD) patients, but that oral iron is a reasonable alternative for CKD patients not undergoing HD. For the latter group of patients, the choice between oral and IV iron is more nuanced. KDIGO advises clinicians to “select the route of iron administration based on the severity of iron deficiency, availability of venous access, response to prior oral iron therapy, side effects with prior oral or IV iron therapy, patient compliance, and cost.” While some studies have noted the potential for serious adverse effects to be greater with IV vs. oral iron, considerations of adherence and effectiveness may encourage use of IV formulations.\textsuperscript{13}

**Newer Oral Iron Agents**

While oral iron has been available for many years, its use has been limited in part by GI side effects including dyspepsia and constipation.\textsuperscript{8} Some of the dyspepsia is thought to arise from
gastric acid interacting with the ferrous (Fe$^{2+}$) form which is more basic than ferric (Fe$^{3+}$) iron. Conversion of Fe$^{2+}$ to Fe$^{3+}$ iron by gastric acid facilitates its absorption even though the Fe$^{3+}$ iron must be reduced back to Fe$^{2+}$ iron by ferrireductase (duodenal cytochrome B or DCYTB) before absorption by the divalent metal transporter 1 (DMT1) channel in the small bowel. That is the rationale for administering Fe$^{2+}$ iron supplements on an empty stomach when gastric acid will not be buffered by food. Novel iron formulations utilize Fe$^{3+}$ iron which does not require administration on an empty stomach, causes less dyspepsia, and bioavailability is not decreased by agents which decrease stomach acidity such as H2-blockers and proton pump inhibitors.

**Ferric Citrate**

Ferric citrate (FC) is a novel oral iron preparation in which the Fe$^{3+}$ iron is complexed to a polymer of tricarboxylic acid (citrate) and water. Originally introduced as a phosphate binder, FC subsequently obtained US Food and Drug Administration (FDA) approval as a treatment for iron-deficiency anemia in CKD without KRT patients. FC vs. placebo was studied in 232 CKD without KRT patients with iron deficiency anemia (IDA) who had failed therapy with iron salts such as ferrous sulfate (FS). A substantially higher percentage of those treated with FC (52.1%) vs. placebo (19.1%, P<0.001) achieved the primary endpoint of 1 g/dL increase in Hb any time during the 16-week randomization period. There was slightly more gastrointestinal toxicity, both diarrhea (24% vs. 19%) and constipation (22% vs. 15%), in FC vs. placebo subjects, respectively. A pooled analysis of the 232 patient phase 3 trial with a 149 patient phase 2 trial of demonstrated that more patients treated with FC achieved Hb >10 (47.8% vs. 18.6% with placebo). This analysis also identified a higher rate of gastrointestinal side effects in the FC arm. A reanalysis of the phase 3 trial showed that patients with more severe iron deficiency experienced a greater increase in Hb. A randomized trial of 60 CKD without KRT patients
found FC to be more effective in increasing TSAT and ferritin at 12 weeks. However, the FC group was prescribed 1260 mg of elemental iron per day vs. 195 mg in the ferrous sulfate group, so the differences may not be surprising even accounting for the 3-4 fold lower bioavailability of ferric iron.\textsuperscript{17,18} Hb levels, as well as a number of other parameters (fibroblast growth factor [FGF]-23, intact parathyroid hormone, and erythroferrone) were not significantly different between the two groups.\textsuperscript{19}

In patients with DD-CKD, FC is indicated for phosphate binding but off-label as an iron supplement. A phase 3 randomized controlled trial of FC vs. sevelamer carbonate and/or calcium acetate in 441 prevalent hemodialysis patients for over one year demonstrated higher median ferritin levels in the FC arm with an average mean difference of 282 ng/mL (P<0.001). TSAT increased in the FC arm by 9.5% (P<0.001). Erythropoiesis stimulating agent (ESA) dose, IV iron requirements, and Hb were all favorably improved in the FC arm to statistical significance with no increase in adverse events.\textsuperscript{20} While the price of FC is higher than other phosphorus binders and oral iron therapies, economic analyses suggest that the reduction in ESA and IV iron requirements would result in a net savings by implementing these therapies.\textsuperscript{21,22} FC reduced serum phosphate levels among patients with CKD without KRT with elevated baseline serum phosphate concentrations (>4.5 mg/dL) but did not reduce serum phosphate among patients with baseline serum phosphate concentrations within the population reference range. FC reduced FGF-23 concentrations to a statistically significant degree (P<0.001) vs. placebo.\textsuperscript{23} A meta-analysis of 16 studies of FC use in patients with CKD demonstrated significant increases in Hb, TSAT, and ferritin vs. comparator.\textsuperscript{24}

Ferric Maltol
Ferric maltol consists of one Fe$^{3+}$ ion complexed to 3 maltol moieties. This structure protects the Fe$^{3+}$ ion while passing through the stomach and provides high bioavailability when the complex is dissociated at the enterocyte, Fe$^{3+}$ iron reduced to Fe$^{2+}$, and then absorbed via DMT-1. As such, a lower dose of iron has been shown to be efficacious with this agent, 30 mg twice daily.$^{25}$ In a placebo-controlled study of 168 CKD without KRT patients studied for 16 weeks, ferric maltol raised hemoglobin by 0.5 ± 0.122 g/dL vs. -0.02 ± 0.165 g/dL (P=0.0149).$^{26}$ In addition to data presented for use in patients with iron deficiency anemia secondary inflammatory bowel disease, these results led to US FDA approval in 2019.$^{27}$

Sucrosomial Iron

The sucrosome is a novel drug delivery method that has been applied to oral iron repletion. Sucrose esterified with fatty acids and combined with lecithin forms a phospholipid bilayer encasing ferric pyrophosphate.$^{28}$ The bilayer is further coated with tricalcium phosphate and starch permitting it to pass through the stomach acid. Downstream it is endocytosed through Peyer’s patch microfold cells (M cells).$^{25}$ The efficacy of sucrosomial iron 30 mg daily was evaluated in a 3-month open-label randomized controlled trial of 99 CKD without KRT patients in comparison to IV sodium ferric gluconate (SFG) 125mg/week until a total dose of 1000mg was administered. At 3 months, the proportion of patients who achieved an increase in Hb of 0.6 g/dL was 56.2% with SFG vs. 43.5% of sucrosomial iron (P<0.05). Fewer adverse events attributed to treatment were seen in the sucrosomial iron group (3.1% vs. 34.5%, P<0.001).$^{25,29}$ Sucrosomial iron (as SiderAL®) is available over the counter in the US through its website and other on-line vendors.

Summary of novel oral irons
Each of the novel agents has improved GI tolerability relative to Fe$^{2+}$ formulations. Sucrosomial iron is a reasonable first choice due to its lower overall cost and availability without a prescription. Ferric maltol is next in cost, while ferric citrate is the costliest but also offers phosphate binding capability (Table 1).

**Newer IV Iron Agents**

The number of IV iron agents has grown steadily in the past few years. Older agents such as iron dextran (1974), SFG (1999) and iron sucrose (IS, 2000), have been joined by ferumoxytol in 2009, and more recently ferric carboxymaltose (FCM) and ferric derisomaltose (FDI, also known as iron isomaltoside). Concerns about oxidative stress induced by rapid iron release,\textsuperscript{30,31} manifested by adverse reactions including cardiovascular events motivated the development of newer compounds.\textsuperscript{32-35}

Modern formulations contain iron enveloped by a carbohydrate moiety that minimizes iron release within the circulation.\textsuperscript{8,30,36} The newer agents have reduced rates of anaphylaxis compared to iron dextran, but ongoing concerns remain surrounding hypersensitivity reactions, cardiovascular events, and hypophosphatemia, which are summarized in Table 2.\textsuperscript{36,37}

**Ferumoxytol**

Because it was approved over a decade ago, ferumoxytol is not considered a newer IV iron agent and will not be discussed in detail in this review. However, it is important to point out that ferumoxytol was the first IV iron agent to both decrease the incidence of anaphylaxis compared to iron dextran and to decrease the intravascular release of free iron compared to SFG and IS. Because the adverse reactions to free iron in the circulation are dose-related, the maximum FDA-
approved single dose of SFG is 125 mg, although it is commonly administered off-label in doses of 250 mg. The maximum FDA-approved single dose of IS is 100mg in DD-CKD patients, 200 mg in non-dialysis dependent CKD patients, and 300-400 mg in peritoneal dialysis patients. For CKD without KRT and home dialysis patients, such a limitation requires several visits to an infusion center to administer a 1000 mg repletion dose of IV iron. This also means more venipunctures for those infusions which puts future vascular access at risk. Ferumoxytol is approved for 510 mg administration by infusion or slow IV push over 15 minutes. It has been reported that 1020 mg ferumoxytol can be safely administered over 15 minutes, thus allowing for iron repletion in a single visit.

**Ferric Carboxymaltose**

Initially approved for use by the FDA in 2013, FCM is composed of ferric oxyhydroxide surrounded and tightly bound by carboxymaltose. FCM is dosed at 15 mg/kg on day 0 and day 7 for individuals up to 50 kg in weight. The original FDA approval was 750 mg/dose times 2 doses for individuals above 50 kg, but in 2021 the FDA approved a single 1000 mg dose in such individuals as an alternative. FCM was compared in two cohorts of patients with IDA with other standard iron therapies by Hb increase between day 0 and day 35. In cohort 1, FCM 1500 mg increased hemoglobin by a mean of 1.57 g/dL vs. 0.80 g/dL (P<0.001) with oral ferrous sulfate. In cohort 2, FCM 1500 mg raised hemoglobin by a mean of 2.90 g/dL vs. 2.16 g/dL (P<0.001) with IV IS 1000 mg. Serious adverse events were not significantly different with FCM vs. comparator.

In REPAIR-IDA, among 2584 patients with CKD without KRT and IDA the mean Hb increase at 56 days was 1.13 g/dL in the FCM (750 mg x 2 doses) group and 0.92 g/dL in the IS (200 mg
x 5 doses) group (95% CI: 0.13–0.28) meeting criteria for noninferiority. Serious adverse events were similar between both groups; FCM recipients had more hypertensive episodes while IS recipients had more hypotension. Hypophosphatemia was identified at greater frequency in the FCM arm. FIND-CKD studied FCM in for 56 weeks in CKD patients without RRT with a primary endpoint of initiation of other anemia intervention (ESA, other iron therapy, or transfusion) or two consecutive Hb levels <10 g/dL. FCM treatment was targeted to either high ferritin (400-600 ng/mL) or low ferritin (100-200 ng/mL) compared with FS in a 1:1:2 ratio. The percentage of participants reaching the primary outcome were 23.5% in the FCM high ferritin arm, 32.2% in the FCM low ferritin arm, and 31.8% in the FS arm. The hazard ratio for the primary endpoint was 0.65 (95% CI: 0.44-0.95; P=0.026) for high-ferritin FCM vs. oral iron. No difference in cardiovascular or infectious adverse events were noted.

Ferric Derisomaltose

Iron isomaltoside was initially approved in Australia in 2017 and later by the US FDA in 2020 after being renamed ferric derisomaltose (FDI). Compositionally, FDI is ferric oxyhydroxide encased in derisomaltose. The FERWON group studied FDI administered as a single 1000 mg dose vs. IS given up to 5 doses of 200 mg over 2 weeks. FERWON-IDA included 1512 patients with diverse etiologies of IDA, whereas FERWON-NEPHRO examined 1538 CKD without RRT patients. Both FERWON trials were randomized 2:1 FDI:IS with co-primary endpoints being efficacy at raising Hb at 8 weeks and serious or severe hypersensitivity reactions. Efficacy was nearly identical between the two agents, raising Hb 2.5 g/dL in both arms of FERWON-IDA and 1.22 g/dL in both arms of FERWON-NEPHRO. Hypersensitivity events were also insignificantly different, with a pooled relative risk difference 0.1% higher in FDI vs. IS. An analysis of 5 of these studies (N=5247) noted that the rate of moderate to severe
hypersensitivity reactions was low across all current IV iron formulations excluding iron dextran, at 0.2-1.7%. The differences between agents were small and confidence intervals overlapped.\textsuperscript{51-53} Another metanalysis (N=8599) examining the risk of serious hypersensitivity reactions among IV iron recipients showed a low rate overall, but lower with FDI than FCM or IS.\textsuperscript{54}

The FDI arms in the combined FERWON studies had 63 events in 50 (2.5%) patients vs. the IS arms with 48 events in 41 (4.1%) patients (P=0.018). Driven by hypertension, congestive heart failure, and atrial fibrillation, the time to first adverse cardiovascular event was also longer with FDI versus IS (P=0.014). While unexpected given the short study duration (8 weeks), this differential could be due to slower mobilization of iron and consequent lesser oxidative stress in the FDI recipients.\textsuperscript{56}

PHOSPHARE-IDA paired randomized controlled trials studied FCM and FDI with respect to hypophosphatemia occurring between baseline and day 35 in patients with IDA and normal renal function.\textsuperscript{53} Serum phosphate <2.0 mg/dL occurred with both agents, but significantly more often with FCM than FDI. Trial A: 7.9% vs. 75.0% (P<0.001), and trial B: 8.1% vs. 73.7% (P<0.001), FDI vs. FCM, respectively. A separate systematic review and meta-analysis showed analogous results for hypophosphatemia (FDI 4% vs. FCM 47%, P<0.001). Normal kidney function, low baseline serum ferritin and TSAT were identified as predictors for hypophosphatemia.\textsuperscript{55, 56}

6H Syndrome

The 6H syndrome (high FGF-23, hypophosphatemia, hyperphosphaturia, hypovitaminosis D, hypocalcemia, and secondary hyperparathyroidism) seen with various IV iron formulations but most prominent with FCM is thought to occur due to impaired cleavage (inactivation) of the phosphatonin FGF-23.\textsuperscript{57, 58} Longer term complications of hypophosphatemic osteomalacia and
fractures have also been described (Figure 2). Clinicians will need to weigh the relative risks, costs, and availability of the various intravenous iron formulations when selecting therapy (Table 3).

**Ferric Pyrophosphate Citrate**

Ferric pyrophosphate citrate (FPC) offers the option to administer iron directly via dialysate bicarbonate containers or bicarbonate central delivery system and was FDA approved for use in hemodialysis (HD) patients in 2015. The iron dose administered with each dialysis is 5-7 mg, which approximates the iron loss with each HD treatment. CRUISE paired trials compared FPC to placebo over 48 weeks and found that Hb levels were maintained with FPC while falling by 0.4 g/dL with placebo (P<0.001). Ferritin and TSAT were more stable in the FPC arm; ESA and IV iron requirements decreased in the FPC arm. Because some dialysis providers are concerned regarding the infection risk of iron in the bicarbonate central delivery system and because some dialysis machines use solid bicarbonate concentrate, an intravenous form of FPC was developed and approved by the FDA in 2020. The IV form is infused over the course of the hemodialysis treatment (pre- or post-membrane) and provides 6.75 mg iron in a prefilled syringe. FPC can be infused using the machine’s heparin pump. If the patient is receiving heparin, FPC can be safely mixed with the heparin.

**Conclusion**

Functional and absolute iron deficiency often contribute to anemia in patients with CKD and iron repletion is required for effective Hb synthesis. Newer oral agents may provide increased iron bioavailability and fewer side effects than traditional iron salts, perhaps decreasing the need for IV iron therapy in some patients with CKD without KRT and on home dialysis. For patients
with milder degrees of iron deficiency (e.g. TSAT >15% and ferritin >50 ng/mL) we propose starting with an inexpensive oral ferrous salt unless the patient reports previous intolerance to such agents. If the patient does not respond in 2-3 months or is intolerant of the Fe\textsuperscript{2+}, then it is reasonable to switch to a newer ferric oral iron supplement or IV iron preparation. If the patient has more severe iron deficiency (TSAT <15% or ferritin <50 ng/mL), we recommend proceeding directly to an IV iron agent. Newer IV iron formulations are associated with fewer anaphylactic reactions than iron dextran and decreased free iron that may contribute to acute reactions and long-term vascular injury. Because these IV iron preparations can be given in larger single doses than ferric gluconate or iron sucrose, there are better suited for patients with CKD without KRT and those on home dialysis to decrease visits to infusion centers and venipuncture. Nonetheless, caution with respect to nuanced risks of IV iron formulations remains prudent due to acute reactions and hypophosphatemia. Newer IV iron agents are expensive and may not be approved by some prescription drug plans. In such cases, we prefer to prescribe 1000 mg of iron dextran in single infusion than to subject the patient to multiple smaller infusions of SFG or IS. It remains to be determined how a shift away from in-center HD for treatment of ESKD as well as more effective therapies to slow the rate of CKD progression, as proposed by the Advancing American Kidney Health Initiative, will accelerate the development and uptake of iron therapies designed to decrease patient travel to infusion centers while maintaining or improving tolerance and safety.

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References:


38. Inc. WP. Ferrlecit (sodium ferric gluconate complex in sucrose injection) NDA. 2006;


## Table 1: Oral Therapies for Iron Repletion in CKD

<table>
<thead>
<tr>
<th>Agent</th>
<th>Ferrous Sulfate</th>
<th>Ferrous Fumarate</th>
<th>Ferrous Gluconate</th>
<th>Ferric Citrate</th>
<th>Ferric Maltol</th>
<th>Sucrosomial Iron</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspepsia</td>
<td>++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Constipation</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Available over the counter?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Phosphate binder</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Approximate minimum Cost (annual, daily iron repletion dose or recommended dose) USD</td>
<td>$10.80</td>
<td>$237.60</td>
<td>$37.60</td>
<td>$8294.40 (recommended dose)</td>
<td>$7200.00 (recommended dose)</td>
<td>$720.00 (recommended dose)</td>
</tr>
</tbody>
</table>

Based on information from Lexicomp.⁶³
Table 2: Newer (Third Generation) IV Iron Formulations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Molecular Wt. (Da)</th>
<th>Max. Weekly Dose (mg)</th>
<th>Minimun Infusion Time (minutes)</th>
<th>Iron Concentration (mg/mL)</th>
<th>Test Dose Required</th>
<th>Black Box Warning</th>
<th>Severe Hypersensitivity</th>
<th>Hypophosphatemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferumoxytol</td>
<td>731,000</td>
<td>510 mg</td>
<td>15</td>
<td>30</td>
<td>No</td>
<td>Yes</td>
<td>0.4%</td>
<td>0.4%</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>150,000</td>
<td>750 or 1000</td>
<td>15</td>
<td>50</td>
<td>No</td>
<td>No</td>
<td>0.1%</td>
<td>~40%</td>
</tr>
<tr>
<td>Ferric derisomaltoside</td>
<td>150,000</td>
<td>1000 or 20/kg if &lt;50kg</td>
<td>15</td>
<td>100</td>
<td>No</td>
<td>No</td>
<td>0.3%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

Based on information from Glaspy et al.,\textsuperscript{56} Balakrishnan et al.,\textsuperscript{64} and Lexicomp.\textsuperscript{63}
Table 3: Pros and Cons of Parenteral Iron Formulations

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron dextran</td>
<td>Lowest cost, can give 1000mg in one dose (off label), low risk of 6H syndrome</td>
<td>High rate of hypersensitivity, requires test dose, requires 1.5 hours of infusion and observation</td>
</tr>
<tr>
<td>Ferric gluconate</td>
<td>Low risk of severe hypersensitivity, low cost, low risk of 6H syndrome</td>
<td>Takes 4-8 doses to administer 1000mg, administer over 1 hour, risk of hypotension</td>
</tr>
<tr>
<td>Iron sucrose</td>
<td>Low risk of severe hypersensitivity, low cost, low risk of 6H syndrome</td>
<td>Takes 3-5 doses to administer 1000mg</td>
</tr>
<tr>
<td>Ferumoxytol</td>
<td>Low incidence of 6H syndrome, Takes 2 doses to administer 1000mg.</td>
<td>Has black box warning for hypersensitivity, higher cost</td>
</tr>
<tr>
<td>Ferric carboxymaltose</td>
<td>Total US approved dose highest (1500mg in 2 doses), low risk of severe hypersensitivity</td>
<td>Highest incidence of 6H syndrome/hypophosphatemia, higher cost</td>
</tr>
<tr>
<td>Ferric derisomaltoside</td>
<td>Highest Single infusion dose (1000mg) in US – only takes one dose, low risk of severe hypersensitivity</td>
<td>1000 or 20/kg if &lt;50kg, risk of 6H syndrome (4%), higher cost, limited availability (?)</td>
</tr>
<tr>
<td>Ferric pyrophosphate citrate</td>
<td>Low risk of severe hypersensitivity, given through dialysate, low risk of 6H syndrome</td>
<td>In-center hemodialysis patients only; for iron maintenance not repletion; risk of hypotension</td>
</tr>
</tbody>
</table>
Box 1: Iron Deficiency in Anemia of CKD: Summary

- Iron deficiency commonly contributes to anemia of chronic kidney disease and is amenable to treatment with newer oral and intravenous therapies.

- Intravenous iron can lead to a number of rare but serious adverse effects, and hypophosphatemia is increasingly recognized as prevalent and potentially serious.

- The choice of iron supplementation should be individualized to the patient and based on convenience, tolerance, cost, and the severity of iron deficiency.
Legends to Figures

Figure 1:

Direct and indirect regulation of systemic iron homeostasis. Iron (Fe) is provided mainly by reticuloendothelial macrophages that recycle iron from senescent red blood cells (RBCs), with a lesser contribution from dietary absorption and other body stores. Iron circulates in the plasma predominantly bound to transferrin (TF) and is stored in cells in the form of ferritin. The liver hormone hepcidin controls systemic iron homeostasis by inducing degradation of the iron exporter ferroportin (FPN) to reduce iron entry into plasma from dietary sources and body stores. Iron deficiency and erythropoietic drive suppress hepcidin production to provide adequate iron for erythropoiesis and other essential functions. Iron and inflammation induce hepcidin to prevent iron overload and limit iron availability to pathogens. Iron induces hepcidin transcription by stimulating liver endothelial cells to produce bone morphogenetic proteins BMP2 and BMP6, which bind to the hepatocyte BMP receptor complex and coreceptor hemojuvelin (HJV) to activate SMAD transcription factors. Iron also induces hepcidin via the hepatocyte iron sensing apparatus involving transferrin receptor 2 (TFR2), transferrin receptor 1 (TFR1), and homeostatic iron regulator protein (HFE). These pathways are all inhibited by iron deficiency, which also increases the activity of transmembrane serine protease 6 (TMPRSS6) to cleave HJV and further suppress hepcidin. Under conditions of accelerated erythropoietic activity, erythropoietin (EPO) induces erythroid progenitor cells to produce erythroferrone (ERFE), which suppresses hepcidin by functioning as a ligand trap to block the BMP signaling pathway. During inflammation, IL-6 and other inflammatory cytokines induce hepcidin transcription directly via a (STAT)-3 binding element in the hepcidin promoter. Hypoxia-inducible factors (HIFs), which are stabilized by low oxygen (O2) and low iron conditions, contribute to iron
homeostasis and erythropoiesis by regulating the production of EPO in the kidney; ferriductase DCYTB and iron transporters FPN and divalent metal transporter 1 (DMT1) in the intestine; and the plasma iron carrier TF. HEPH, hephaestin; HO, heme oxygenase; HRG, heme transporter HRG1. Image ©2021 Elsevier, Inc, reproduced from Babitt et al. with permission of the copyright holder.

Figure 2:
6H Syndrome. In the setting of iron deficiency, FGF-23 transcription is increased. Normally, this has no substantial adverse consequences because FGF-23 is cleaved proportional to synthesis to the inactive form. However, higher levels of intact FGF-23 develop in the presence of certain IV iron formulations. It is speculated that the carbohydrate moieties of the iron formulations inhibit the cleavage of FGF-23. The extent of this apparent inhibition, and consequent hypophosphatemia, appears to be greatest with ferric carboxymaltose (FCM), substantially less with ferric derisomalose (FDI), lesser still with iron sucrose (IS), and extremely uncommon with ferumoxytol (FER) and iron dextran (ID). Estimates of relative incidence of hypophosphatemia are limited by lack of head to head comparisons across agents and heterogeneity in thresholds of hypophosphatemia, when reported, among studies. Increased FGF-23 leads to enhanced urinary phosphate wasting, lowering serum phosphorus and leading to weakness and fatigue. Increased FGF-23 also reduces 1,25 dihydroxyvitamin D levels resulting in decreased serum calcium. Low calcium may contribute to weakness and fatigue and more importantly causes increased parathyroid hormone. Increased rates of osteomalacia and atypical fractures have been reported principally with ferric carboxymaltose to date. Based on information from Kassianides et al, Blumenstein et al, and Glaspy et al.
Pathophysiology and Biochemical Abnormalities

Iron Deficiency

Carbohydrate moieties from FCM > FDI > IS > FER ≈ ID

↑ Intact FGF-23

↓ FGF 23 Cleavage

↓ Cleaved FGF-23

Complications

↓ Urinary phosphate wasting

↓ 1,25 (OH)₂ Vitamin D₃

↓ Serum Calcium

↑ Parathyroid Hormone

Weakness

Fatigue

↓ Serum Phosphorus

Osteomalacia

Atypical Fractures

Weakness

Fatigue

↓ Serum Phosphorus