IV iron formulations and use in adults

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Intravenous iron has become a major component of the therapeutic armamentarium for iron deficiency and iron deficiency anemia. The earliest formulations were associated with unacceptable toxicity. Newer formulations, with complex carbohydrate cores that bind elemental iron more tightly, allow the administration of full therapeutic doses in 15 to 60 minutes. Nonetheless, a folklore of danger, fueled by earlier formulations no longer available, continues to foment caution. Complement-mediated minor infusion reactions, referred to as complement activation-related pseudo-allergy, resolve without therapy. Inappropriate intervention with vasopressors and H_1 blockers converts these minor reactions into hemodynamically significant adverse events. Four new formulations, low-molecular-weight iron dextran, ferumoxytol, ferric carboxymaltose, and ferric derisomaltose, all approved for the treatment of iron deficiency in a host of conditions, are now widely used with an excellent safety profile. Herein, the administration, safety, indications, and management of infusion reactions are discussed. Treatment-emergent hypophosphatemia, a newly recognized side effect for some formulations, is also reviewed. Based on the preponderance of published evidence, intravenous iron should be moved up-front for the treatment of iron deficiency and iron deficiency anemia in those conditions in which oral iron is suboptimal.

LEARNING OBJECTIVES

- Debunk an antiquated folklore of danger associated with intravenous iron formulations
- Recognize infusion reactions and their management
- Become familiar with the administration of the 4 formulations of intravenous iron capable of complete replacement (total dose infusion) in 15 to 60 minutes

CLINICAL CASE

A nulliparous woman is referred for fatigue, pagophagia, and inability to sleep due to constant uncomfortable feelings in the legs while lying down. Menses have been intermittently heavy, lasting 7 days with clot passage and flooding. The hemoglobin concentration is 10 g/dL with a platelet count of 620 000/uL. Serum ferritin is 11 ng/mL, and transferrin saturation (TSAT) is 9%. Ferrous sulfate ($FeSO_4$) containing 60 mg of elemental iron was prescribed on alternate days. Gastric irritation and constipation occurred. She was referred to hematology, and 1000 mg of low-molecular-weight iron dextran (LMWID) was ordered over 60 minutes. Forty seconds after a slow start, chest pressure and flushing occur. She experiences no hypotension, wheezing, stridor, or periorbital edema.

Introduction

It has been nearly a century since Heath injected subcutaneous and intramuscular iron, reporting hemoglobin increments in hypochromic anemias (Figure 1).[1] In the early 20th century, an attempt to administer intravenous iron as colloidal ferric hydroxide resulted in toxicity so severe as to "preclude its use for therapeutic purposes."[2] Undoubtedly, the observed toxicity was provoked by prohibitive levels of labile-free iron after the administration of a formulation with virtually no ability to bind elemental iron. However, in 1954 Baird and Padmore introduced iron dextran for intramuscular and intravenous injections, observing rapid hematologic responses with few serious adverse events (SAEs).[3] Infusion reactions abounded, resulting in perceptions of anaphylaxis. Intravenous iron continued to be infrequently prescribed until the 1990s when recombinant erythropoietin was released for dialysis-associated anemia, requiring intravenous iron as an adjuvant for optimal response.[4]

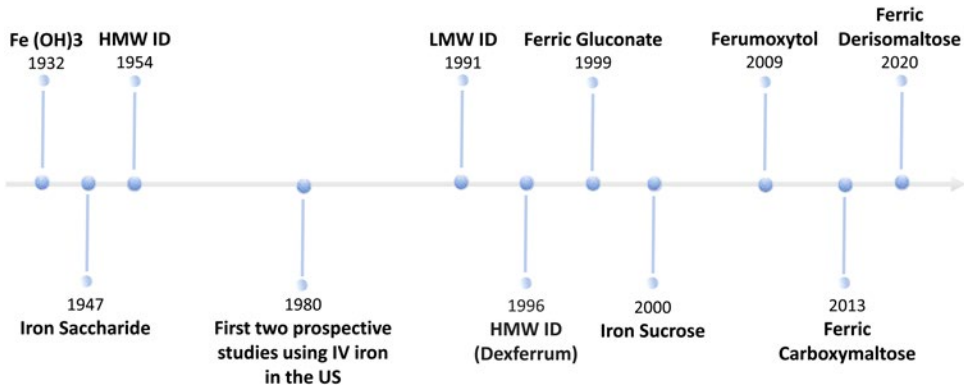

Figure 1. History of intravenous iron in the United States.

Today we know that the preponderance of AEs occurring with intravenous iron are minor reactions to labile-free iron, likely complement mediated and self-limited, resolving without therapy. Anaphylaxis is rare, occurring in fewer than 1 in 200 000 administrations.[5] A folklore of danger persists, driven by the alarming incidence of SAEs caused by a formulation of high-molecular-weight iron dextran (HMWID) no longer available, along with imprudent administration of vasopressors and antihistamines for minor reactions, converting them into hemodynamically significant SAEs. Publications using indirect surrogates for anaphylaxis such as spontaneous AE reporting,[6] medical claims,[7,8] and sales data perpetuate this concern.[9,10] These surrogates are unable to distinguish inappropriate intervention for minor reactions from SAEs. This position is supported by thousands of patients in head-to-head studies reporting no difference in safety or efficacy among the available products.[11,12]

Herein we report the pharmacology of 6 available formulations of intravenous iron, its administration, and its indications in a host of conditions associated with iron deficiency (ID). These include ferric gluconate (FG), iron sucrose (IS), LMWID, ferumoxytol, ferric carboxymaltose (FCM), and ferric derisomaltose (FDI) (Table 1). Following infusion, all share a similar fate. The iron carbohydrate complexes mix with plasma and are phagocytosed within the reticuloendothelial system, wherein the carbohydrate shell is degraded, and iron is stored as ferritin or transported out of the cell, bound to transferrin, which delivers iron to its destiny.[13]

The formulations are similar in structure, with an iron core surrounded by a carbohydrate shell, excluding FDI, which is a matrix structure. They differ in the physicochemical properties of size, labile iron content, and release of iron in the serum.[14] Labile iron derives from bound iron within the nanoparticle and is readily mobilized by chemical reactions or proteins.[14] All formulations have the potential to cause infusion reactions from labile-free iron dependent on dose, speed of infusion, and formulation stability (Figure 2).[15] FG and IS, with much smaller cores releasing larger amounts of labile-free iron, require lower doses and more frequent visits to achieve the therapeutic dose.[14] Accordingly, these formulations are not discussed further, and discussions of formulations are limited to the 4 able to be administered as full doses in 15 to 60 minutes. We hope these data debunk the myths of danger, leading to increased use of this necessary treatment for the most frequent maladies we as hematologists see in our work, ID and ID anemia.

Safety

The initial response to parenteral iron was once so negative that it is remarkable we have this opportunity to demonstrate the ease of administering new formulations that allow for the complete correction of ID in 15 to 60 minutes. The perception of danger was so ingrained that although the first large prospective study of intravenous iron reported only three SAEs without residua or hospitalization in 481 patients who received 2099 doses of intravenous HMWID, the authors concluded that intravenous iron should be reserved for situations in which oral iron cannot be used, and the need for replacement is urgent.[16]

A decade later the release of erythropoietin for dialysis-associated anemia fostered new interest in intravenous iron. LMWID (INFed) was released in 1991 and became standard for dialysis-associated anemia.[17] Unfortunately, a HMWID, Dexferrum (Vifor), was released as a less expensive alternative to LMWID and resulted in an alarming increase in reactions.[5] With this formulation's removal from the pharmacopoeia and the release of two iron salts, FG and IS, SAEs became rare. This position was corroborated by a systematic review and meta-

Table 1. Intravenous iron formulations

Trade name Manufacturer Carbohydrate	INFeD-US Cosmofer-Europe AbbVie low-molecular-weight iron dextran	Feraheme Covis Ferumoxytol	Injectafer-US Ferinject-Europe Daiichi Sankyo Carboxymaltose	Monoferric Pharmacosmos Derisomaltose
Total dose infusion **Test dose required** **Approved dose**	Yes Yes 100 mg per dose	No No 510 mg	Yes- Europe/No- US No 1000 mg Europe 750 mg US	Yes No 20 mg/kg (1000 mg if >66 kg)
Optimal dose **Infusion time**	1000 mg 60 minutes	1020 mg 30 minutes	1000 mg Europe/750 mg × 2 US 15 minutes	1000 mg 20 minutes

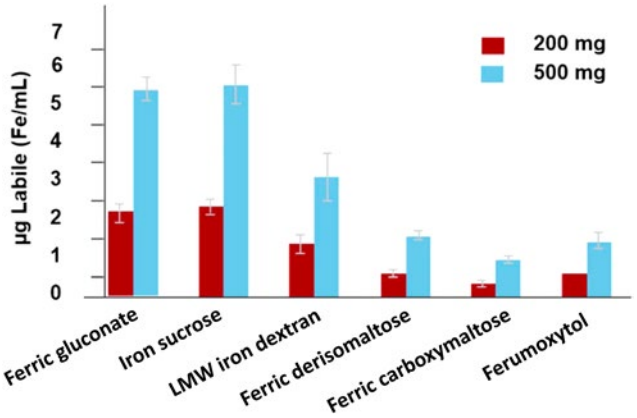

Figure 2. Labile iron by iron formulation. Labile-free iron is elemental iron that has been released from the core of the iron/carbohydrate nanoparticle and available to bind transferrin. All formulations have the potential to cause infusion reactions from labile-free iron. The higher the labile iron content, the greater the likelihood of CARPA. FG and IS, with much smaller cores, releasing larger amounts of labile-free iron, require lower doses and more frequent visits to achieve the therapeutic dose. Reprinted from Jahn et al.[14] with permission.

analysis reviewing 103 trials including 10 390 patients treated with IV iron compared with 4044 with oral iron, 1329 with no iron, 3335 with a placebo, and 155 with intramuscular iron (a route now proscribed).[12] While infusion reactions occurred, intravenous iron was not associated with an increased risk of SAEs or infections. This conclusion was proven by the largest and longest prospective trial ever performed. A cohort of 2141 adults undergoing hemodialysis were randomized to intravenous iron administered proactively (400 mg/mo targeting ferritin of >700 ug/L or TSAT >40%) or reactively (0–400 mg/mo when ferritin was <200 ug/L or TSAT <20%).[18] After a mean 2.1-year follow-up, the proactive regimen was not only noninferior but resulted in lower doses of erythropoiesis stimulating agents for the same clinical outcome, leading to significant cost savings. Cardiovascular outcomes were superior in the proactive arm. Corroborating the meta-analysis,[12] as expected no increase in infections was observed.

The preponderance of perceived SAEs are not immunoglobulin E (IgE)–mediated hypersensitivity reactions but complement activation–related pseudo-allergy (CARPA). CARPA is characterized by complement-mediated activation by nanoparticles of free or labile iron that do not bind quickly enough to transferrin.[19] Mast cells and basophils are triggered by compliment activation that resembles true IgE-mediated allergy.[20] This reaction is not specific to intravenous iron and has been recognized with monoclonal antibodies and liposomal medications.[21] CARPA can occur any time, does not require prior sensitization, and is dependent on infusion rate. This not infrequently occurring and quickly resolving reaction is non–life-threatening and characterized by flushing, myalgias and/or arthralgias, back pain, and/or chest pressure.[21] No symptoms of anaphylaxis are present.[20,22] These reactions are self-limited, and diphenhydramine should be avoided as it can worsen symptoms (Figure 3).[23] Rechallenge at a slower rate with the same formulation is appropriate,[24] as well as caution against intervening with vasopressors and antihistamines, which can convert minor reactions into SAEs.[21,25]

CLINICAL CASE (continued)

Within 4 minutes symptoms resolve. Methylprednisolone and famotidine are administered empirically as prophylaxis. The remaining planned dose is administered seamlessly over 30 minutes. The pagophagia disappears immediately, and the restless leg syndrome resolves that evening. Within 48 hours energy levels improve.

Formulations

Multiple head-to-head studies among the formulations have failed to report a significant difference in efficacy, infusion reactions, or safety. Subsequently, the discussion assumes equality.

Low-molecular-weight iron dextran

LMWID was approved in the United States in 1991. Millions of doses have been administered in dialysis-associated anemia,[5] non–dialysis dependent chronic kidney disease (CKD),[26] pregnancy,[27] heavy menstrual bleeding,[26] and a host of other conditions associated with ID without a safety signal. Nonetheless, unfounded concerns regarding anaphylaxis persist. LMWID can be administered as a single 1000-mg infusion over 1 hour.[26] LMWID was used in the first study of IV iron in cancer-associated anemia.[28] In this study 157 subjects were randomized to LMWID, oral, or no iron. The administration of LMWID resulted in greater hemoglobin (1 g/dL) and hematopoietic (2 g/dL) responses with reduced times to targets (with concomitant decrements in erythropoiesis stimulating agents) compared with oral and no iron. Intravenous iron resulted in consistently improved quality-of-life parameters.

LMWID was used in the first US prospective study evaluating IV iron in pregnancy.[27] Seventy-three gravidas received 1000 mg of LMWID. No SAEs were observed, and no negative infant outcomes were reported. The authors concluded that compared with oral iron, intravenous iron has less toxicity and is more effective in increasing hemoglobin, supporting moving it closer to frontline therapy in iron-deficient pregnant patients.

LMWID carries a black box warning of risk of severe, sometimes fatal anaphylactic reactions and requires a 25-mg test dose.[29] This warning stems from antiquated notions of danger that are discredited. Nonetheless, we recommend starting slowly and observing for 10 to 15 minutes. Following a brief observation, the remainder should be administered over the balance of 1 hour.

Ferumoxytol

Ferumoxytol was the first new formulation allowing rapid infusion (20-30 minutes) of a complete dose. In 1981 the company Advanced Magnetics, led by physicists and physical chemists, designed a compound intended as a magnetic resonance imaging (MRI) contrast agent.[30] Ferumoxytol is a superparamagnetic iron oxide linked to polyglucosesorbitol carboxymethylether.[31] A rapid injection of 510 mg in 17 seconds, consistent with the administration of radiologic contrast agents, was recommended.

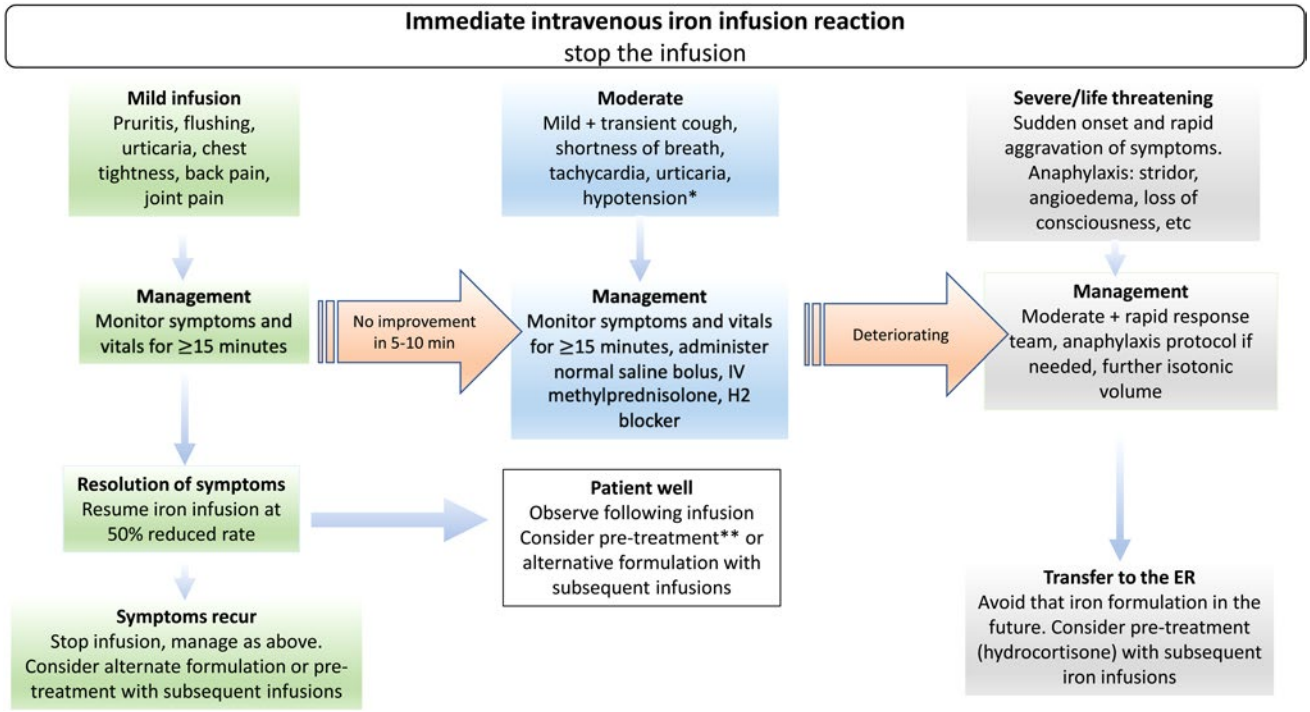

Figure 3. Management of acute intravenous iron infusion reactions. *Hypotension is defined as a drop of 30 mmHg or more in systolic blood pressure from baseline or systolic blood pressure of equal to or less than 90 mmHg. **Methylprednisolone 125 mg plus or minus H2 antihistamine. We avoid first-generation H1 antihistamines (eg, diphenhydramine), as this can cause somnolence, tachycardia diaphoresis, and sometimes hypotension, mimicking an anaphylactic reaction. The majority of SAEs can be attributed to the use of diphenhydramine and/or epinephrine for the management of immediate infusion reactions. Adapted from Rampton et al.[20]

Serendipitously, significant improvements in hemoglobin concentrations were observed, leading to its investigation as an iron replacement therapy. In 2009 it was approved for the correction of ID with CKD. As a result of its function as an MRI contrast agent, if an MRI is planned within 8 weeks of administration, radiologists must be notified of its presence so that interpretation is not confounded.[32]

The 17-second injection was implemented, and retrospectively, while labile-free iron is markedly reduced with ferumoxytol compared to IS and FG,[14] an alarming number of reactions occurred. Even allowing for the Weber effect (increased reporting whenever new products are launched), reactions were frequent and mistaken for anaphylaxis.[33] While we now know these were likely CARPA, the number of reports of AEs to the US Food and Drug Administration (FDA) was so high a black box warning was issued. This resulted in failure to obtain a broad label for other causes of ID, limiting its use. The label stipulated a minimum infusion rate of 510 mg over 15 minutes. Support for the imprudence of rapid administration comes from one of our practices (MA). The first 90 doses administered over 17 seconds were associated with 3 episodes of hypotension that resolved rapidly without sequelae. Serum tryptase levels were normal, suggesting these were not anaphylactic reactions.[34] Upon slowing the rate to 3 minutes, more than 2500 doses were administered without clinically significant AEs. Nonetheless, we recommend following the 15-minute infusion rate, consistent with recommendations for the other 2 new parenteral iron formulations, FCM and FDI.

To address hypersensitivity, in 2017 the manufacturer of ferumoxytol performed a randomized, double-blind comparison to FCM.[35] The methods, which were FDA mandated to approve a broad label for ferumoxytol for ID, required two 510-mg infusions of ferumoxytol 1 week apart compared with two 750-mg infusions of FCM 1 week apart, each over 15 minutes. While a 50% difference in dose may seem obtuse, this iteration compared 2 existing approved methods. Of 1997 patients, 997 received ferumoxytol and 1000, FCM. No difference in reactions was observed. As expected, there was more hypophosphatemia with FCM (discussed further under treatment-emergent hypophosphatemia). No clinical sequelae secondary to hypophosphatemia were reported. Hypophosphatemia was not observed with ferumoxytol. These results were also consistent with the randomized trial of ferumoxytol and IS, which evaluated 162 patients, reporting comparable efficacy and AE rates.[36]

Consistent with the data, ferumoxytol received broad FDA approval for the treatment of ID. The approval remained consistent with the existing label requiring 2 infusions of 510 mg over 15 minutes, 1 week apart. However, there was no reason to believe ferumoxytol could not be administered more conveniently, as a single infusion of 1020 mg. Several studies corroborate this position.[37,38] We routinely administer 1020 mg in 250-mL normal saline over 30 minutes with no observed SAEs in more than 2000 infusions and are currently conducting a randomized, double-blind, double-dummy trial of oral and IV iron in patients after bariatric surgery using the single-dose

method.[39] It is our hope that these data will foster the approval of 1020 mg of ferumoxytol as a single infusion.

Recently a generic of ferumoxytol (Sandoz) was approved. To date there are no safety data. In the initial filing with the FDA for generic approval, the results of 60 patients were submitted. Minor infusion reactions were increased compared with published data on the brand. Multiple institutions have reported increased infusion reactions with the generic. We recommend caution with its use.

Ferric carboxymaltose

Like ferumoxytol, FCM infusion results in limited labile-free iron.[40] FCM was first licensed in Europe as Ferinject (Vifor Pharma) in 2007. In its initial filing in the United States, concerns around hypophosphatemia and adverse cardiac events delayed the approval for nearly 2 years. It received broad-label approval from the FDA in 2013.[41] It is a macromolecular ferric hydroxide carbohydrate complex allowing a single dose of 1000 mg in Europe or 2 doses of 750 mg in the United States in 15 to 20 minutes.[42] FCM is effective in patients with heavy uterine bleeding,[43] inflammatory bowel disease,[44,45] chemotherapy-induced anemia,[46] and pregnancy.[47,48]

Notably, FCM was the first formulation to definitively report the benefits of intravenous iron in heart failure (HF) and ID.[49,50] The definitive FAIR-HF trial resulted in significant improvements with intravenous iron independent of hemoglobin, supporting the correction of ID in patients with HF. These data were corroborated by the CONFIRM-trial with a similar design, supporting the benefits of intravenous iron in this population with no safety signal.[49,50]

While FCM results in the least labile-free iron of the intravenous formulations,[14] treatment-emergent hypophosphatemia has come to be most associated with its use,[35,51] which is discussed below.

Ferric derisomaltose

FDI has a short linear structure of linked glucose units forming a unique carbohydrate matrix, binding elemental iron similarly to ferumoxytol and FCM, limiting the release of labile-free iron and allowing large doses to be administered in 15 to 20 minutes.[52] It was approved in Europe in 2009, Canada in 2017, and the United States in 2020 for administration in patients with ID intolerant of, or refractory to, oral iron.

In a randomized, open-label, multicenter trial, FDI compared with IS with coprimary end points adjudicated serious hypersensitivity reactions and a change in hemoglobin from baseline to week 8. The trial consisted of 1512 patients, who were randomized 2 to 1 to a single 1000-mg infusion of FDI or IS administered as 200-mg IV injections, up to 5 times.[53] No difference in safety was observed, and the coprimary efficacy end point for noninferiority in hemoglobin change was met, with a more rapid hemoglobin response observed with FDI. FDI, 1000 mg in 20 minutes, is a more convenient method of IV iron administration than IS, without sacrificing efficacy or safety.

Two similar randomized, open-label trials comparing the safety and efficacy of FDI and IS in non–dialysis dependent CKD randomized over 3000 patients to a single 1000-mg infusion of FDI or multiple infusions of IS.[54,55] The coprimary end points were safety (FDA recommended based on low risks of severe reactions with either) and a change in hemoglobin. Adjudicated AEs and hemoglobin concentrations at week 8 were similar, meeting the coprimary end points.

In a prospective comparison of FDI to usual care in 1137 patients with HF and reduced ejection fraction,[56] similar to that

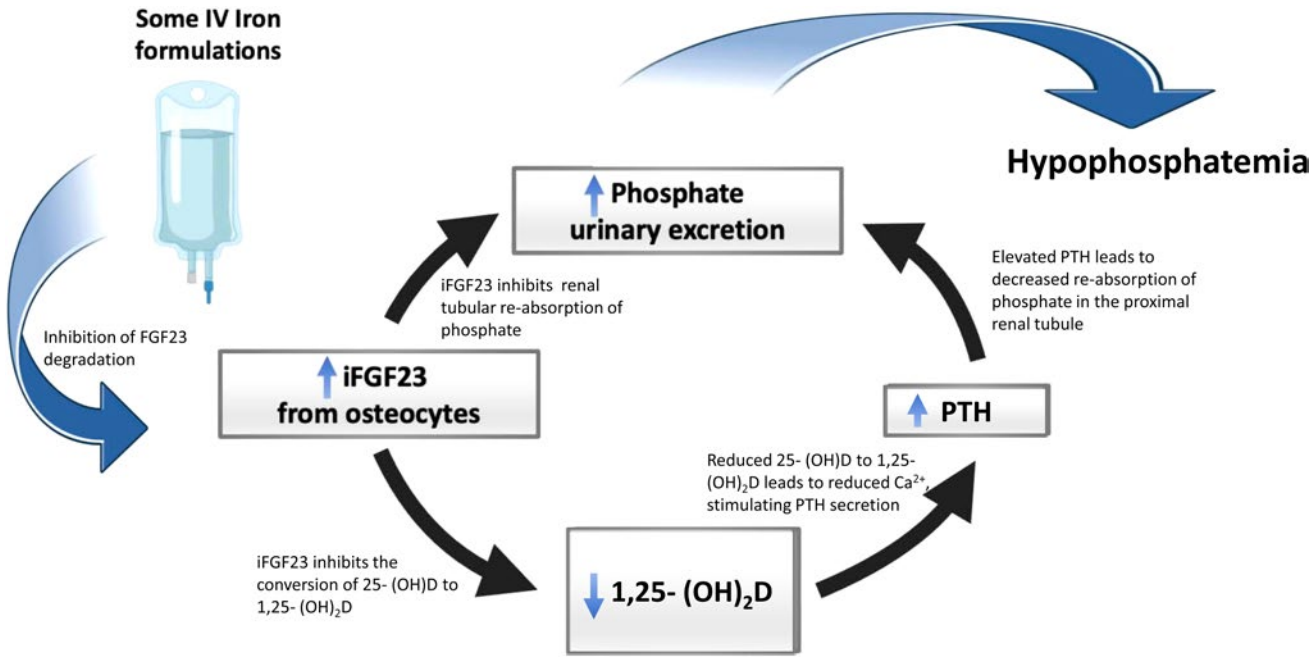

Figure 4. Mechanism of treatment-emergent hypophosphatemia. Following the administration of some intravenous iron formulations is a sharp rise in the plasma iFGF23, triggering a pathophysiological cascade of renal phosphate wasting, calcitriol deficiency, and secondary hyperparathyroidism. This frequently culminates in hypophosphatemia even after iFGF23 levels have normalized. PTH, parathyroid hormone.

reported with FCM, FDI administration resulted in fewer admissions to the hospital as well as a decrease in cardiovascular deaths. The data corroborate the benefit of intravenous iron for patients with HF and ID.

FDI administered as a single 1000-mg infusion has been shown to be safe and effective in ID with CKD,[55] in IBD after bariatric surgery,[57,58] for heavy uterine bleeding, and during both pregnancy and the postpartum period.[59,60] FDI should be administered as a 1000-mg infusion diluted in 100mL of normal saline over 20 minutes.

Treatment-emergent hypophosphatemia

Systematic reviews,[61] meta-analyses,[51,62] and clinical trials have associated some iron preparations with treatment-emergent hypophosphatemia, with incidence, severity, and duration of hypophosphatemia highest following administration of FCM.[35,63-65F] The mechanism of hypophosphatemia following administration is renal wasting regulated by the phosphoturic hormone fibroblast growth factor 23 (FGF23) (Figure 4).[66,67] Following administration, hyperphosphaturic hypophosphatemia triggered by high intact FGF23 (iFGF23) culminates in low 1,25 $(OH)^2$ vitamin D, hypocalcemia, and secondary hyperparathyroidism, which has been associated with osteomalacia, fracture, and other bone deformities.[68] The specific physicochemical properties of FCM likely trigger the sharp increases in iFGF23.[69] This "6-H syndrome" is characterized by 1) high FGF23, 2) hyperphosphaturia, 3) hypophosphatemia, 4) hypovitaminosis D, 5) hypocalcemia, and 6) secondary hyperparathyroidism.[57,70] In extreme cases, hypophosphatemia following FCM has been associated with osteomalacia, fractures, and other bone deformities.[68]

Providers should have a high suspicion of hypophosphatemia in patients who present with worsening fatigue following FCM administration and, consistent with its new label, monitor phosphorus.

Conclusion

The use of intravenous iron to treat a host of common ailments that cause ID and IDA has increased. These conditions include heavy menstrual bleeding and angiodysplasia (hereditary hemorrhagic telangiectasia) in which oral iron cannot keep up with the losses, second- and third-trimester pregnancy in which oral iron does not keep up with the requirements of the growing fetus, bariatric surgery in which oral iron is not absorbed after the procedure, inflammatory bowel disease in which oral iron worsens the underlying pathology, and comorbid conditions (cancer and chemotherapy-induced anemia, CKD) in which IV, and not oral iron, is able to bypass the hepcidin block. Medical personnel often cite safety as a barrier to the use of intravenous iron (internal data). There are an abundance of data supporting the safety of intravenous iron. The majority of infusion reactions are minor, which can be converted into SAEs with unnecessary intervention. It is time to embrace a total dose infusion of intravenous iron in 15 to 60 minutes as frontline therapy for most causes of iron deficiency.

Conflict-of-interest disclosure

Layla Van Doren: honoraria: Pharmacosmos, Daiichi Sanyko.
Michael Auerbach: honoraria: Pharmacosmos. I have received research funding for data management from Covis.

Off-label drug use

Layla Van Doren: There are two off-label uses (based on US label). These off-label uses are covered in Table 1: the recommendation to give LMW ID as a 1000 mg one hour infusion and the recommendation to administer ferumoxytol as a 1020 mg infusion in 30 minutes instead of the current label to give it as 510 mg twice on different days.
Michael Auerbach: There are two off-label uses (based on US label). These off-label uses are covered in Table 1: the recommendation to give LMW ID as a 1000 mg one hour infusion and the recommendation to administer ferumoxytol as a 1020 mg infusion in 30 minutes instead of the current label to give it as 510 mg twice on different days.

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DOI 10.1182/hematology.2023000495