Journal of Blood Medicine

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Ferumoxytol: a silver lining in the treatment of anemia of chronic kidney disease or another dark cloud?

Journal of Blood Medicine downloaded from https://www.dovepress.com/ by 3.238.190.82 on 26-Nov-2020
For personal use only.

This article was published in the following Dove Press journal:
Journal of Blood Medicine
28 August 2012
Number of times this article has been viewed

Amy Barton Pai
Adinoyi O Garba

Albany College of Pharmacy and Health Sciences, Albany, New York, NY, USA

Abstract: Intravenous iron therapy is pivotal in the treatment of anemia of chronic kidney disease to optimize the response of hemoglobin to erythropoiesis-stimulating agents. Intravenous iron use in patients with chronic kidney disease is on the rise. Recent clinical trial data prompting safety concerns regarding the use of erythropoiesis-stimulating agents has stimulated new US Food and Drug Administration label changes and restrictions for these agents, and has encouraged more aggressive use of intravenous iron. The currently available intravenous iron products differ with regard to the stability of the iron-carbohydrate complex and potential to induce hypersensitivity reactions. Ferumoxytol is a newer large molecular weight intravenous iron formulation that is a colloidal iron oxide nanoparticle suspension coated with polyglucose sorbitol carboxymethyl ether. Ferumoxytol has robust iron-carbohydrate complex stability with minimal dissociation or appearance of free iron in the serum, allowing the drug to be given in relatively large doses with a rapid rate of administration. Clinical trials have demonstrated the superior efficacy of ferumoxytol versus oral iron with minimal adverse effects. However, recent postmarketing data have demonstrated a risk of hypersensitivity that has prompted new changes to the product information mandated by the Food and Drug Administration. Additionally, the long-term safety of this agent has not been evaluated, and its place in the treatment of anemia of chronic kidney disease has not been fully elucidated.

Keywords: iron, ferumoxytol, oxidative stress, safety, kidney disease

Anemia of chronic kidney disease

Chronic kidney disease (CKD) is a worldwide public health care epidemic. In the US, progression of CKD to end-stage renal disease (ESRD) is predicted to affect 775,000 people by the year 2020.[1] Since the introduction of epoietin alfa in 1990, intravenous iron has been a pivotal component of the management of anemia of CKD, particularly among patients with ESRD receiving hemodialysis. Intravenous iron supplementation is administered to optimize red blood cell production by erythropoiesis-stimulating agents to reach target hemoglobin concentrations in patients with ESRD on hemodialysis.[2] Intravenous iron use in ESRD has increased steadily over the past 10 years. The new prospective payment system (eg, "bundled" payment) was initiated by the Centers for Medicaid and Medicare Services on January 1, 2011.[3] The new bundled payment reimburses hemodialysis units at a composite rate, comprised of dialysis treatment, laboratory services, and drugs, whereas the latter two items were formerly billed separately. Erythropoiesis-stimulating agents are markedly more expensive than intravenous iron products, and recent data have confirmed increased intravenous iron use since implementation of the new prospective payment system.[4,5] This likely represents a growing

Correspondence: Amy Barton Pai
Albany Nephrology Pharmacy Group-ANephRx, Albany College of Pharmacy and Health Sciences, 106 New Scotland Avenue, Albany, NY 12208, USA
Tel +1 518 694 7203
Fax +1 518 694 7382
Email amy.bartonpai@acphs.edu

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/JBM.S29204

© 2012 Barton Pai and Garba, publisher and licensee Dove Medical Press Ltd. This is an Open Access article which permits unrestricted noncommercial use, provided the original work is properly cited.

Journal of Blood Medicine downloaded from https://www.dovepress.com/ by 3.238.190.82 on 26-Nov-2020
For personal use only.

trend towards more aggressive use of intravenous iron products in lieu of more expensive erythropoiesis-stimulating agents to meet Centers for Medicare and Medicaid Services performance measures (hemoglobin 10–12 g/dL). Among the pre-ESRD population (ie, CKD stages 3–5), recent clinical trial data suggesting an unfavorable mortality risk in patients receiving erythropoiesis-stimulating agents, especially with aggressive hemoglobin targeting, has driven a trend of using intravenous iron first-line in this growing population.[6–8] Further, oral iron is generally poorly tolerated and has limited efficacy.[9,10]

However, a logistic issue presents itself in this population because intravenous iron cannot be administered as conveniently as in hemodialysis patients who can have intravenous iron administered during their in-center dialysis three times per week. This has created interest in intravenous iron with physicochemical properties that would allow larger doses to be administered less frequently in an outpatient clinic setting and where cost savings could be realized.[11] In summary, the complicated evidence base and reimbursement climate has spurred aggressive intravenous iron use in patients with ESRD as well as CKD and not on dialysis. Thus, it remains critically important to understand the efficacy and safety profiles of newer intravenous iron products. This review addresses the efficacy and safety considerations of ferumoxytol, a newer large molecular weight intravenous iron compound.

Dysfunctional iron metabolism in anemia of CKD

An estimated 90% of hemodialysis patients have fluctuating hemoglobin patterns.[12] This hemoglobin variability has been attributed to resistance to erythropoiesis-stimulating agents, characterized by not reaching target hemoglobin goals despite high doses of these agents, eg, >400,000 units of epoietin alfa per month. Resistance to erythropoiesis-stimulating agents is also characterized by blockade of the reticuloendothelial system, impairing iron mobilization. Clinically, blockade of the reticuloendothelial system manifests as high serum ferritin, usually coincident with low saturated transferrin concentrations, indicating impaired mobilization and transfer of iron. Other causes of resistance to erythropoiesis-stimulating agents include chronic oxidative stress and inflammation, and, more recently, upregulation of hepcidin.[13,14]

Hepcidin is a small peptide hormone induced by proinflammatory cytokines, principally interleukin-6.[15] The hormone acts to sequester iron by activating cell signaling pathways that stimulate ferroportin internalization in hepatocytes acting as a negative regulator of iron absorption and release.[15] Plasma hepcidin concentrations have been found to be elevated in several observational studies of patients with CKD and to increase proportionately along the continuum of CKD.[16,17] Mitigating sources of inflammation, such as chronic periodontitis, were associated with a significant reduction of prohepcidin, interleukin-6, and C-reactive protein in a small pilot study.[17] No improvement in hemoglobin response was observed after antimicrobial treatment for periodontitis. Thus, although hepcidin is elevated in patients with CKD, its utility as a biomarker to predict response to intravenous iron and erythropoiesis-stimulating agents remains to be elucidated.[18,19]

Physicochemical properties of ferumoxytol

Ferumoxytol is described as an iron oxide nanoparticle with a polyglucose sorbitol carboxymethyl ether coating reportedly designed to minimize immunological sensitivity.[20] Its physiochemical properties result in less free iron in vitro than other available intravenous iron preparations.[21] Ferumoxytol consists of superparamagnetic iron oxide coated with a carbohydrate shell consisting of branched polysaccharides, which helps to isolate bioactive iron from plasma components until the iron-carbohydrate complex enters macrophages in the reticuloendothelial system of the liver, spleen, and bone marrow.[22] The molecular weight of ferumoxytol is estimated to be 731 kDa, with a colloidal nanoparticle diameter of 30 nm.[21] Recently, Jahn et al showed an additional peak for ferumoxytol at smaller nanoparticle sizes (about 11 nm diameter) in a gel permeation chromatography experiment to determine particle distribution by weight for various intravenous iron products.[23] When compared with other parenteral iron products, the relative molecular weight of ferumoxytol is as follows: ferumoxytol > iron dextran > iron sucrose > sodium ferric gluconate (see Table 1). Of these formulations, only ferumoxytol was found to be isotonic in a study comparing the physicochemical properties of ferumoxytol with commercially available products in the US.[21] Free (unbound) iron appearance was measured by ultrafiltration and by the bleomycin-detectable iron assay to determine potential direct donation of free iron to transferrin and free iron potentially available to engage in redox reactions, respectively.[21] Removal of ferumoxytol by an in vitro hemodialysis circuit was also investigated. The relative iron release, catalytic iron availability, and dialysis removal of these intravenous iron formulations were as follows: ferumoxytol < iron dextran < iron sucrose < ferric gluconate. These data suggest

Table 1 Comparison of properties of ferumoxytol and those of other intravenous iron formulations

Properties	FMX	FCM	IM[c]	ID[d]	IS	FG
Molecular weight (Da)[a]	731,000	150,000[b]	150,000‡	410,000	252,000[e]	200,000
Carbohydrate shell[b]	Polyglucose sorbitol carboxymethyl ether*	Carboxymaltose	Isomaltoside	Dextran polysaccharide	Sucrose	Gluconate, loosely associated sucrose
Median shell/particle diameter (nm)[c]	26.3	23.1	20.5	12.2	8.3	8.6
Relative catalytic iron release[a,c,f]	+	+§	+	++	+++	+++
Relative stability of elemental iron within the carbohydrate shell[a]	High	High	High	High	Medium	Low
Relative osmolalities[a,g]	Isotonic	Isotonic	N/A	Isotonic†	Hypertonic	Hypertonic
Administration (intravenous push) rates[b]	30 mg/sec	Bolus push	50 mg/min	50 mg (1 mL)/min	About 20 mg/min	12.5 mg/min
Maximum single dose[b,c]	510 mg	15 mg/kg	20 mg/kg	20 mg/kg	200 mg	125 mg
Half-life (hours)[b]	About 15	7–12	5–20	5–20	6	~about 1

Notes: [a]Balakrishnan et al,[21] release of catalytic Fe measured by bleomycin-detectable iron assay in a nonclinical model (5 minutes post injection); [b]from USP package insert/prescribing information; [c]Jahn et al,[23] shell particle diameter was measured by dynamic light scattering; [d]data listed are for low molecular weight iron dextran, unless stated otherwise; [e]package insert/prescribing information states the molecular weight of iron sucrose (Venofer®) to be 34,000–60,000 Da; [f]Pai et al[43] showed that nontransferrin bound iron levels were significantly higher in patients on iron sucrose and FG versus ID; [g]Funk et al[51] compared physical and pharmacological properties of FCM with other intravenous iron products [+ (Fe ≤ 0.02 μg/mL); ++ (Fe > 0.02 to ≤0.04 μg/mL), +++ (>0.04 μg/mL)]. *A modified dextran shell;[47] †Balakrishnan et al,[21] low molecular weight iron dextran had a slightly hypertonic osmolality (500 mOsmol/kg); §free (dialyzable) iron was 0.002% in buffered solution but was elevated by 100× in normal saline (Jahn et al[23]); ‡apparent molecular weight as measured by gel permeation chromatography (Jahn et al[23]).

Abbreviations: FMX, ferumoxytol; FCM, ferric carboxymaltose; IM, iron isomaltoside 1000; ID, iron dextran; FG, ferric gluconate; Fe, iron; IS, iron sucrose; IV, intravenous.

Journal of Blood Medicine downloaded from https://www.dovepress.com/ by 3.238.190.82 on 26-Nov-2020
For personal use only.

superior iron-carbohydrate complex stability than that in currently available intravenous iron preparations.[21]

Pharmacokinetics

The recommended dosing for ferumoxytol is 510 mg intravenous initially and a second dose of 510 mg administered 3–8 days later.[22] The stability of ferumoxytol enables it to be administered as a rapid intravenous bolus injected at a rate up to 1 mL (30 mg) per second. Previous pharmacokinetic studies of other commonly used intravenous iron compounds have examined changes in the iron pool using conventional measures of iron status, including serum iron and transferrin-bound iron.[24] Some studies have used ratios derived from ex vivo analyses of serum samples to determine serum iron versus iron from the iron-carbohydrate complex.[25] These methods render the pharmacokinetic profile of the drug difficult to interpret because they do not directly measure the plasma concentration or differentiate disposition of the iron-carbohydrate complex from endogenous iron concentrations. In contrast, plasma ferumoxytol concentrations are determined using a validated, drug-specific, nuclear magnetic resonance assay.[26] Due to the superparamagnetic properties of ferumoxytol, this bioanalytical method allows for measurement of iron in the intact drug product before its incorporation into iron stores. Thus, exact determination of the pharmacokinetic profile of ferumoxytol can be made. Ferumoxytol exhibits zero-order or Michaelis-Menten (capacity-limited) pharmacokinetics.[27] Thus, handling of the drug by the reticuloendothelial system is saturable and the drug will remain in plasma until such time that the concentration is below the saturation concentration and the reticuloendothelial system can resume handling the drug linearly. A randomized, double-blind, ascending-dose study was conducted in healthy volunteers (n = 41) receiving 1, 2, or 4 mg Fe/kg, and 4 mg Fe/kg administered at different rates, with the half-life of ferumoxytol increased with increasing dose from 9.3 to 14.5 hours but not with increasing rate of injection using a constant dose.[28] Clearance also decreased, while the area under the concentration-time curve increased with increasing dose, indicating that handling by the reticuloendothelial system is saturable and that the drug follows zero-order pharmacokinetics. However, in this study, linear (first-order) pharmacokinetic analysis was performed, generating erroneous pharmacokinetic parameters.

In a more recent pharmacokinetic study conducted in 58 healthy volunteers, 510 mg of ferumoxytol was administered in two consecutive doses separated by a 24-hour interval.[27] The resulting data suggested that a two-compartment, capacity-limited (zero-order) elimination model was most appropriate. The mean ± standard error population V_{max} (maximal elimination rate from plasma) was 14.3 ± 1.3 mg/hour. Because interindividual plasma concentrations showed minimal variability, the final parameter estimates were used to simulate a typical two-dose regimen (2 × 510 mg 24 hours apart) to predict linear pharmacokinetic parameters. The day 2 maximal plasma concentration was 281 μg/mL, consistent with the measured value. The terminal half-life was estimated to be about 15.8 hours.

Journal of Blood Medicine downloaded from https://www.dovepress.com/ by 3.238.190.82 on 26-Nov-2020
For personal use only.

Efficacy

Clinical trials have shown ferumoxytol to be efficacious in increasing hemoglobin, transferrin saturation, and ferritin in patients with anemia of CKD. In a prospective, open-label, Phase II dose-escalation trial to evaluate the safety and efficacy of ferumoxytol, a two-dose regimen of ferumoxytol was shown to increase hemoglobin and transferrin saturation levels significantly from baseline.[20] In two separate, open-label, randomized, controlled, multicenter Phase III trials in patients with CKD, ferumoxytol significantly increased hemoglobin, transferrin saturation, and ferritin when compared with oral iron.[29,30] These studies and their key outcomes are summarized in Table 2.

There is a lack of published head-to-head trials comparing ferumoxytol with other intravenous iron formulations. Recently, Strauss et al presented preliminary data comparing the hemoglobin response in patients with CKD treated with ferumoxytol versus iron sucrose in FIRST (the Ferumoxytol Compared to Iron Sucrose Trial).[31] The study included patients with all stages of CKD (Stages 1–5D). One hundred and sixty-two patients were randomized to receive ferumoxytol (n = 80) or iron sucrose (n = 82). Ferumoxytol was administered as two consecutive 510 mg doses, while iron sucrose was administered as 100 mg × 10 doses in hemodialysis patients and 200 mg × 5 doses over 14 days in nondialysis patients with CKD. At the end of the 35-day follow-up period, the patients treated with ferumoxytol and those treated with iron sucrose had similar increases in hemoglobin concentrations (0.84 g/dL versus 0.74 g/dL, respectively, $P = 0.515$). Subgroup analysis of patients with more severe anemia (hemoglobin 7–9 g/dL) showed that 50% of those receiving ferumoxytol had an increase in hemoglobin $\geq$ 1 g/dL from baseline versus 40% of those receiving iron sucrose. However, neither standard deviations nor statistical analyses were presented with these data.[30]

Safety and tolerability

Immunogenicity

Data from Phase II and III clinical trials overall showed a very favorable safety profile for ferumoxytol (Table 2). In a large, randomized, multicenter, double-blind, placebo-controlled, crossover Phase III safety study, 750 patients with CKD were assigned to receive 510 mg of ferumoxytol over 17 seconds followed by the alternative agent (saline as placebo or vice versa) 7 days later.[31] The total number of reported adverse events was 242 for ferumoxytol and 178 for placebo. Serious adverse events were reported for 21 ferumoxytol-treated patients and for 15 placebo-treated patients. Of the total adverse events reported, 95 were considered to be related to treatment, as determined by the site investigator (5.2% for ferumoxytol treatment and 4.5% for placebo). One serious adverse event was documented as being related to ferumoxytol, and was recorded in an 85-year-old male with multiple drug allergies (although notably, allergy to two or more drugs was an exclusion criterion for the study) who experienced severe hypotension, hot flashes, and itching a few minutes after receiving ferumoxytol. Dyspnea was not reported and the patient's symptoms resolved after administration of subcutaneous epinephrine. After ferumoxytol was approved by the US Food and Drug Administration (FDA) on June 30, 2009, postmarketing reports of serious hypersensitivity reactions, including those of an anaphylactic type, some of which were life-threatening or fatal, began appearing in the literature and in reports to the FDA.[22,33,34] It is important to note that patients with multiple drug sensitivities (ie, not just to intravenous iron) were excluded from all Phase II and III trials.[29,30] Patients with multiple drug allergy syndrome are well known to be at high risk of hypersensitivity reactions to subsequent chemically unrelated drugs.[35]

The product information for ferumoxytol describes the drug as "a superparamagnetic iron oxide coated with polyglucose sorbitol carboxymethyl ether" (Description) and as a "superparamagnetic iron oxide coated with a carbohydrate shell" (Mechanism of Action).[21] Data published prior to FDA approval contain descriptions of ferumoxytol as an iron oxide core stabilized by carboxymethylated dextran ligands.[36,37] These data infer that the carbohydrate coating contains branched-chain polysaccharides that may be associated with immunogenicity. A recent case report described a 77-year-old woman with stage 4 CKD who had a previous allergic-type reaction to iron dextran 8 months earlier characterized by dyspnea, hypotension, and back pain.[34] Twenty minutes after a single dose of ferumoxytol 510 mg injected over one minute, the patient experienced pruritus on her abdomen and thighs, dyspnea, wheezing, emesis, and tongue swelling. She developed hypotension and required oxygen due to an oxygen saturation drop to about 80%. Laboratory measurement of tryptase, a marker of mast cell activation, was elevated to 22.9 ng/mL (normal $<$ 11.5 ng/mL), providing compelling evidence that this was an anaphylactoid-type reaction. Bailie et al recently analyzed data obtained via the FDA Freedom of Information Act regarding adverse events reported to the FDA during the period from June 2009 to October 2010 for all available intravenous iron products available in the US.[33] These included iron sucrose (Venofer®), sodium ferric gluconate (Ferrlecit®), high molecular weight

Journal of Blood Medicine downloaded from https://www.dovepress.com/ by 3.238.190.82 on 26-Nov-2020
For personal use only.

Table 2 Summary of safety and efficacy data from key clinical trials

Authors	Study type	Patient characteristics	Treatment groups	Outcome at follow-up	*P* value[a]	Reported adverse events
Spinowitz et al[20]	Phase II	CKD patients with Hgb ≤ 12.5 g/dL and TSAT ≤ 35%	4 doses of 255 mg FMX (each dose 2–3 days apart) n = 10 or	Hemoglobin: 10.4 ± 1.3 g/dL increased to 11.4 ± 1.2 g/dL	$P < 0.05$[b]	All ADRs were described as mild[c]: constipation Delayed pruritic edematous rash Pain at injection site
		(n = 21)	2 doses of 510 mg (each dose one week apart) n = 11	TSAT: 21.3% ± 10% increased to 37.2% ± 22.1%	<0.05[b]	
Spinowitz et al[29]	Phase III	Patients with CKD with Hgb ≤ 11 g/dL, ferritin ≤ 600 ng/mL, and TSAT ≤ 30%	2 doses of FMX 510 mg IV (about a week apart) n = 228 or	Hgb: increase by 0.82 ± 1.24 g/dL (FMX) versus 0.16 ± 1.02 g/dL (oral iron)	<0.0001	292 patients were included in the safety analysis Treatment-related ADRs: 10.6% (FMX) versus 24% (oral iron)
		(n = 304)	200 mg oral iron daily for 21 days n = 76	Ferritin: increase by 381.7 ± 278.6 ng/dL (FMX) versus 6.9 ± 60.1 ng/dL (oral iron)	<0.0001	The most common ADRs in the FMX group: Nausea (1.8%)
				TSAT: increase by 9.8% ± 9.2% (FMX) versus 1.3% ± 6.4% (oral iron)	<0.0001	Dizziness (1.8%) Diarrhea (1.4%) Injection site swelling (0.9%)
Provenzano et al[30]	Phase III	CKD stage 5 patients on HD ≥ 90 days, hemoglobin ≤ 11.5 g/dL, ferritin ≤ 600 ng/mL, TSAT ≤ 30%, and at stable ESA doses for at least 10 days prior to study	2 doses of FMX 510 mg IV (about a week apart) n = 114 or	Hgb: increased by 1.02 ± 1.13 g/dL (FMX) versus 0.46 ± 1.06 g/dL (oral iron)	0.0002	110 patients were included in the safety analysis[d] Treatment-related ADRs: 8.2% (FMX) versus 15.9% (oral iron)
		(n = 230)	200 mg oral iron daily for 21 days n = 116	Ferritin: increase by 233.9 ± 206.9 ng/dL (FMX) versus −59.23 ± 106.22 ng/dL (oral iron)	<0.0001	Serious ADRs in the FMX group (n = 54): Hypotension (3.7%) Cellulitis (3.7%)
				TSAT: increase by 6.44% ± 12.59% (FMX) versus 0.55% ± 8.34% (oral iron)	<0.0001	COPD exacerbation (3.7%)

Notes: [a]Significant changes from baseline at follow-up on day-35; [b]significant difference in cumulative Hgb and TSAT of both groups at day 14; [c]this study did not provide the frequency of ADRs; [d]represents only safety data from the randomized phase of this study.

Abbreviations: ADR, adverse drug reaction; COPD, chronic obstructive pulmonary disease; HD, hemodialysis; Hgb, hemoglobin; ESA, erythropoiesis-stimulating agents; FMX, ferumoxytol; IV, intravenous; TSAT, transferrin saturation.

Journal of Blood Medicine downloaded from https://www.dovepress.com/ by 3.238.190.82 on 26-Nov-2020
For personal use only.

iron dextran (Dexferrum®), low molecular weight iron dextran (InFed®), and ferumoxytol (Feraheme®). Because of the large discrepancy in market share during the study time period (iron sucrose > sodium ferric gluconate > low molecular weight iron dextran > high molecular weight iron dextran > ferumoxytol), adverse event rates were calculated both as rates per million units of drug sold and per rates per million 100 mg dose equivalents of intravenous iron. A total of 197 reports were submitted to the FDA for intravenous iron during the study period. Of these, 88 (44.7%) cited ferumoxytol. The highest numbers of reported deaths were with ferumoxytol (n = 6) and low molecular weight iron dextran (n = 5), and the highest number of reported adverse events cited ferumoxytol (n = 70). The adverse event rate for ferumoxytol reported as per million units sold was 50 and rate per million 100 mg dose equivalents of intravenous iron was ten. In comparison, adverse event rates for low molecular weight iron dextran, an agent known to be associated with hypersensitivity reactions, were 4.5 per million units sold and 4.5 per 100 mg dose equivalents. Risk analysis using calculated odds ratios for adverse events classified as deaths, serious adverse events, other major adverse events, or other adverse events clearly showed that ferumoxytol was associated with the highest risk for adverse events of all types. For example, the odds ratio for ferumoxytol was 155-fold higher for death than the odds ratio calculated for iron sucrose. There are several limitations to the interpretation of these data, including the Weber effect, a phenomenon which states that the number of reported adverse reactions for a drug increases until the middle to end of the second year of marketing. However, these data do suggest that further evaluation and vigilant monitoring of patients receiving ferumoxytol is warranted. Post marketing, the product information for ferumoxytol was modified in November 2010, June 2011, and November 2011 to incorporate additional information into the Warnings and Precautions and Adverse Reactions sections, noting the risk of hypersensitivity reactions and including a requirement to "observe the patient for signs and symptoms of hypersensitivity during and after Feraheme® administration for at least 30 minutes and until clinically stable following completion of each administration".[22] The current product information still lists the infusion rate at 30 mg per second (510 mg over 17 seconds), and although administration over one minute has been proposed to improve tolerability,[38] the nature of the reaction being anaphylactoid (not requiring IgE activation and can occur with first dose) versus anaphylactic argues against advocating for this extended administration time because the reaction is not dose-related and could occur at anytime during therapy.

Free iron appearance, oxidative stress, and organ toxicity

Patients with CKD are considered to be in a chronic inflammatory state.[39] Oxidative stress is a key factor linking inflammation and cellular damage, resulting in development and progression of atypical cardiovascular disease in these patients.[39,40] Patients with CKD have several risk factors that place them at a higher risk of oxidative stress including age, obesity, diabetes, hypertension, and reduced antioxidant capacity.[39] The hemodialysis process itself also induces oxidative stress, especially via immune activation through dialyzer contact and endotoxin challenge from dialysate.[40] Thus, patients with CKD are at high risk of the deleterious consequences of pro-oxidant stimuli and have reduced intracellular and extracellular defenses to ameliorate free radical damage. Modern intravenous iron formulations have evolved to be comprised of iron oxide cores encased in protective carbohydrate shells. These carbohydrate moieties "shield" the iron core, allowing for safe delivery to the reticuloendothelial system and preventing direct release of iron into the plasma.[41] Free iron is an important regulator of cell signaling in the Fenton-Haber-Weiss reaction whereby ferric iron is reduced to ferrous iron in the presence of hydrogen peroxide, yielding a hydroxide radical, which is a highly reactive oxygen species.[42] Because of potential toxicity, free iron is tightly regulated and has several important physiological roles in the body, including involvement in mitochondrial electron transport, cytochrome P450 activity, and transfer of oxygen by heme. The efficacy of these carbohydrate molecules in shielding iron and preventing iron-based free radical and cytotoxic reactions is variable and dependent on the size of the carbohydrate shell (eg, molecular weight of the iron-carbohydrate complex).[42] Short-term studies indicate all available formulations are capable of generating free unbound iron which is released directly into the circulation from the iron-carbohydrate complex. However, there is a clear relationship between stability of the complex and appearance of free iron, with the likely rank order based on evaluable data being sodium ferric gluconate > iron sucrose > low molecular weight iron dextran > ferumoxytol = ferric carboxymaltose = iron maltoside 1000.[21,23,43–45] Production of oxygen-based free radicals from iron-induced redox reactions can damage any tissue, protein, lipid, or RNA/DNA in close proximity of the free radical.

Journal of Blood Medicine downloaded from https://www.dovepress.com/ by 3.238.190.82 on 26-Nov-2020
For personal use only.

Using both in vitro and in vivo models, Johnson et al investigated the relative renal toxicity profiles of iron sucrose, sodium ferric gluconate, and ferumoxytol in a model of acute renal failure. In isolated human kidney proximal tubule cell experiments, doses of elemental iron at 500 μg/mL (relevant to clinically achievable plasma concentrations) were studied to determine the effects of the three different intravenous iron products.[46] Cell viability was significantly reduced by iron sucrose but not by sodium ferric gluconate or ferumoxytol. Release of lactate dehydrogenase, a marker of cytotoxicity, was evaluated in proximal tubule cells incubated for 60 minutes with 2 mg/mL of each of the three products and was found to increase significantly after exposure to iron sucrose and sodium ferric gluconate, but not after exposure to ferumoxytol ($P < 0.001$ for both agents). In the in vivo studies, 2 mg of each of the intravenous iron products was administered to CD-1 mice which were sacrificed 3 hours following administration, at which time renal tissue and plasma were collected. There were no significant changes in renal monocyte chemoattractant protein (MCP-1) mRNA, a marker stimulated by pro-oxidant signaling, in mice exposed to iron sucrose or sodium ferric gluconate, while ferumoxytol-treated animals were noted to show downregulation of MCP-1 mRNA. Similarly, plasma MCP-1 increased significantly only in mice treated with iron sucrose or sodium ferric gluconate. The same experiment was repeated with evaluation of renal tissue and plasma 18 hours post intravenous iron administration. Renal neutrophil gelatinase-associated lipoprotein and mRNA, markers of acute kidney injury, were noted to be significantly elevated in both the iron sucrose and sodium ferric gluconate groups, with no change observed after exposure to ferumoxytol. Collectively, these data suggest that because ferumoxytol is a robust and stable compound, it may not have a high potential to induce oxidative stress in the kidney.[46] In contrast with the study by Johnson et al, a recent in vivo study compared 40 mg/kg of ferumoxytol with ferric carboxymaltose, low molecular weight iron dextran, and iron sucrose in rats, evaluating oxidative stress parameters in the liver, heart, and kidneys.[47] Doses of intravenous iron products were administered by tail vein injection every 7 days for a total of five doses, and the animals were sacrificed 24 hours after the last intravenous iron dose. In animals exposed to iron sucrose, low molecular weight iron dextran, and ferumoxytol, hepatic Kupffer cells showed positive Prussian blue staining, indicating intracellular deposition of iron. Low molecular weight iron dextran had more extensive liver deposition, with deposits also observed in hepatocytes and sinusoidal endothelial cells. Serum liver function tests were also noted to be significantly elevated with ferumoxytol and low molecular weight iron dextran treatment as early as 24 hours after the first dose. Beginning on day 15, rats treated with ferumoxytol or low molecular weight iron dextran showed increased urinary protein excretion, and at days 22 and 29, ferumoxytol-treated animals showed significantly higher protein excretion than any of the other intravenous iron treatments. Clinical trials have noted an association between intravenous iron and increased proteinuria, generating concern about use in patients with CKD not on dialysis.[48] Expression of proinflammatory cytokines, ie, tumor necrosis factor alpha and interleukin-6, was increased significantly in immunostained liver and kidney tissue in ferumoxytol-treated animals. Taken together, these studies underscore a need to investigate and understand thoroughly the safety and toxicity profiles of larger molecular weight iron-carbohydrate complexes, such as ferumoxytol, because iron-induced oxidative stress may extend beyond simple dissociation of free iron.

Ferumoxytol is the only commercially available intravenous iron product with an iron oxide core consisting of a colloidal dispersion of nanoparticles ranging from about 11 nm to 30 nm in size.[21,23] Nanoparticles are known to undergo avid uptake by the reticuloendothelial system, resulting in hepatic, splenic, and lymph node iron accumulation, a characteristic exploited for magnetic resonance imaging.[49] Weissleder et al examined the pharmacokinetic and toxicity profiles of AMI-25, a superparamagnetic iron oxide nanoparticle formulation similar to ferumoxytol that was labeled with a ^{59}Fe tracer to evaluate tissue disposition in the liver, spleen, kidney, lung, and brain.[49] The compound rapidly accumulated in the liver and was cleared slowly, with a half-life estimated at 3 days. Notably, the authors stated that the average patient would receive 80 mg for magnetic resonance imaging, which would produce liver concentrations estimated at 212 μg/g wet weight, well below the toxic concentrations associated with hepatocellular carcinoma (4000 μg/g) in liver deposition disorders. However, a dose of approximately 1500 mg of this compound (a clinically relevant dose of ferumoxytol) would produce liver concentrations of 4000 μg/g, at least transiently. The biodynamics of iron oxide nanoparticles vary depending on particle diameter, with mean superparamagnetic iron oxide particle diameters of 75 nm and ultrasmall superparamagnetic iron oxide particle diameters of 18 nm.[50] Ultrasmall superparamagnetic iron oxides are often not immediately recognized by the reticuloendothelial system, thus prolonging intravascular half-life.[50] These features, which are unique to superparamagnetic iron oxides like ferumoxytol,

Journal of Blood Medicine downloaded from https://www.dovepress.com/ by 3.238.190.82 on 26-Nov-2020
For personal use only.

may produce different toxicity profiles, particularly at the cellular level, and warrant further investigation.

Summary

Ferumoxytol is a novel intravenous iron formulation approved for iron deficiency in adult patients with chronic kidney disease. The robust stability of the iron-carbohydrate complex allows for rapid intravenous administration of large doses of elemental iron (approximately 500 mg). However, post-marketing FDA reports and cases appearing in the literature have raised significant concern regarding hypersensitivity reactions, likely related to the modified dextran-carbohydrate coating surrounding the iron oxide core. Clinical trial data have reported similar adverse event rates to placebo; however, no study has adequately evaluated other risks, such as iron-induced oxidative stress. Although ferumoxytol is associated with minimal appearance of free iron, in vitro and animal studies suggest higher rates of tissue iron deposition and toxicity relative to other available smaller molecular weight intravenous iron compounds. This may be due in part to its unique colloidal nanoparticle structure. In summary, ferumoxytol is a newer intravenous iron product with demonstrated efficacy. However, safety concerns remain, and the place of ferumoxytol in therapy has not been established.

Disclosure

The authors report no conflicts of interest in this work.

References

1. United States Renal Data Systems. *2011 Annual Data Report*. Bethesda, MD: National Institutes of Health, National Institute of Diabetes, Digestive, and Kidney Diseases; 2011.
2. Kidney Disease Outcomes Quality Initiative. Clinical Practice Guideline and Clinical Practice Recommendations for anemia in chronic kidney disease: 2007 update of hemoglobin target. *Am J Kidney Dis*. 2007;50:471–530.
3. Department of Health and Human Services, Centers for Medicare and Medicaid Services Medicare and Medicaid Programs; Conditions for Coverage for End-Stage Renal Disease Facilities, Final Rule. 42 CFR Parts 405, 410, 413, 414, 488, and 494. Available from: http://www.cms.gov/CFCsAndCoPs/downloads/ESRDfinalrule0415.pdf. Accessed January 27, 2012.
4. Robinson BM, Fuller DS, Bieber BA, Turenne MN, Pisoni RL. The DOPPS Practice Monitor for US dialysis care: trends through Apr 2011. *Am J Kidney Dis*. 2012;59:309–312.
5. Cardone KE, Fox B, Meola S, et al. Effects of the ESRD Medicare Bundling Rule on Anemia Management in Private Dialysis Units. Presented at the American Society of Nephrology Renal Week, November 8–13, 2011, Philadelphia, PA.
6. Singh AK, Szczech L, Tang KL, et al; CHOIR Investigators. Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med*. 2006;355:2085–2098.
7. Drüeke TB, Locatelli F, Clyne N, et al; CREATE Investigators. Normalization of hemoglobin level in patients with chronic kidney disease and anemia. *N Engl J Med*. 2006;355:2071–2084.
8. Pfeffer MA, Burdmann EA, Chen CY, et al; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. *N Engl J Med*. 2009;361:2019–2032.
9. Kidney Disease: Improving Global Outcomes Anemia Work Group. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2:279–335.
10. Albaramki J, Hodson EM, Craig JC, Webster AC. Parenteral versus oral iron therapy for adults and children with chronic kidney disease. *Cochrane Database Syst Rev*. 2012;1:CD007857.
11. Bhandari S, Naudeer S. Improving efficiency and value in health care. Intravenous iron management for anaemia associated with chronic kidney disease: linking treatment to an outpatient clinic, optimizing service provision and patient choice. *J Eval Clin Pract*. 2008;14:996–1001.
12. Gilbertson DT, Ebben JP, Foley RN, et al. Hemoglobin level variability: associations with mortality. *Clin J Am Soc Nephrol*. 2008;3:133–138.
13. de Francisco AL, Stenvinkel P, Vaulont S. Inflammation and its impact on anaemia in chronic kidney disease: from haemoglobin variability to hyporesponsiveness. *NDT Plus*. 2009;2 Suppl 1:i18–i26.
14. Kanbay M, Perazella MA, Kasapoglu B, Koroglu M, Covic A. Erythropoiesis stimulatory agent-resistant anemia in dialysis patients: review of causes and management. *Blood Purif*. 2010;29:1–12.
15. Nemeth E, Ganz T. The role of hepcidin in iron metabolism. *Acta Haematol*. 2009;122(2–3):78–86.
16. Zaritsky J, Young B, Wang H-J, et al. Hepcidin-A potential biomarker for iron status in chronic kidney disease. *Clin J Am Soc Nephrol*. 2009;4:1051–1056.
17. Vilela EM, Bastos JA, Fernandes N, Ferreira AP, Chaoubah A, Bastos MG. Treatment of chronic periodontitis decreases serum prohepcidin levels in patients with chronic kidney disease. *Clinics (Sao Paolo)*. 2011;66:657–662.
18. Ford KI, Eby CS, Scott MG, Coyne DW. Intra-individual variability in serum hepcidin precludes its use as a marker of iron status in hemodialysis patients. *Kidney Int*. 2010;78:769–773.
19. Tessitore N, Girelli D, Campostrini N, et al. Hepcidin is not a useful biomarker for iron needs in hemodialysis patients on maintenance erythropoiesis-stimulating agents. *Nephrol Dial Transplant*. 2010;25:3996–4002.
20. Spinowitz BS, Schwenk MH, Jacobs PM, et al. The safety and efficacy of ferumoxytol therapy in anemic chronic kidney disease patients. *Kidney Int*. 2005;68:1801–1807.
21. Balakrishnan VS, Rao M, Kausz AT, et al. Physicochemical properties of ferumoxytol, a new intravenous iron preparation. *Eur J Clin Invest*. 2009;39:489–496.
22. Feraheme™ (ferumoxytol) injection prescribing information. Lexington, MA: AMAG Pharmaceuticals Inc; 2010.
23. Jahn MR, Andreasen HS, Futterer S, et al. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer®), a new intravenous iron preparation and its clinical implications. *Eur J Pharm Biopharm*. 2011;78:480–491.
24. Seligman PA, Dahl NV, Strobos J, et al. Single-dose pharmacokinetics of sodium ferric gluconate complex in iron-deficient subjects. *Pharmacotherapy*. 2004;24:574–583.
25. Danielson BG, Salmonson T, Derendorf H, Geisser P. Pharmacokinetics of iron(III)-hydroxide sucrose complex after a single intravenous dose in healthy volunteers. *Arzneimittelforschung*. 1996;46:615–621.
26. McLachlan SJ, Morris MR, Lucas MA, et al. Phase I clinical evaluation of a new iron oxide MR contrast agent. *J Magn Reson Imaging*. 1994;4:301–307.
27. Pai AB, Nielsen JC, Kausz A, Miller P, Owen JS. Plasma pharmacokinetics of two consecutive doses of ferumoxytol in healthy subjects. *Clin Pharmacol Ther*. 2010;88:237–242.
28. Landry R, Jacobs PM, Davis R, Shenouda M, Bolton WK. Pharmacokinetic study of ferumoxytol: a new iron replacement therapy in normal subjects and hemodialysis patients. *Am J Nephrol*. 2005;25:400–410.
29. Spinowitz BS, Kausz AT, Baptista J, et al. Ferumoxytol for treating iron deficiency anemia in CKD. *J Am Soc Nephrol*. 2008;19:1599–1605.

Journal of Blood Medicine downloaded from https://www.dovepress.com/ by 3.238.190.82 on 26-Nov-2020
For personal use only.

30. Provenzano R, Schiller B, Rao M, Coyne D, Brenner L, Pereira BJ. Ferumoxytol as an intravenous iron replacement therapy in hemodialysis patients. *Clin J Am Soc Nephrol*. 2009;4:386–393.
31. Strauss W, Li J, McLaughlin, et al. Differential hemoglobin response following treatment with two IV irons in patients on hemodialysis or with more severe anemia: results from the ferumoxytol compared to iron sucrose trial (FIRST). Abstract 49 presented at the National Kidney Foundation Spring Clinical Meeting, May 9–13, 2012, Washington, DC.
32. Singh A, Patel T, Hertel J, Bernardo M, Kausz A, Brenner L. Safety of ferumoxytol in patients with anemia and CKD. *Am J Kidney Dis*. 2008;52:907–995.
33. Bailie GR. Comparison of rates of reported adverse events associated with IV iron products in the United States. *Am J Health Syst Pharm*. 2012;69:310–320.
34. Santosh S, Podaralla P, Miller B. Anaphylaxis with elevated tryptase after administration of intravenous ferumoxytol. *NDT Plus*. 2010;1322:13–14.
35. Asero R. Multiple drug allergy syndrome: a distinct clinical entity. *Curr Allergy Rep*. 2001;1:18–22.
36. Groman EV, Paul KG, Frigo TB, Benegele H, Lewis JM. Heat stable colloidal iron oxides coated with reduced carbohydrates and carbohydrate derivatives. US Patent 6,599,498. July 29, 2007. United States.
37. Simon GH, von Vopelius-Feldt J, Fu Y, et al. Ultrasmall supraparamagnetic iron oxide-enhanced magnetic resonance imaging of antigen-induced arthritis: a comparative study between SHU 555 C, ferumoxtran-10, and ferumoxytol. *Invest Radiol*. 2006;41:45–51.
38. Rosner MH, Auerbach M. Ferumoxytol for the treatment of iron deficiency. *Expert Rev Hematol*. 2011;4:399–406.
39. Himmelfarb J, Stenvinkel P, Ikizler TA, Hakim RM. The elephant in uremia: oxidant stress as a unifying concept of cardiovascular disease in uremia. *Kidney Int*. 2002;62:1524–1538.
40. Del Vecchio L, Locatelli F, Carini M. What we know about oxidative stress in patients with chronic kidney disease on dialysis clinical effects, potential treatment, and prevention. *Semin Dial*. 2011;24:56–64.
41. Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol*. 2004;15:S93–S98.
42. Jomova K, Valko M. Importance of iron chelation in free radical-induced oxidative stress and human disease. *Curr Pharm Des*. 2011;17:3460–3473.
43. Pai AB, Boyd AV, McQuade CR, Harford A, Norenberg JP, Zager PG. Comparison of oxidative stress markers after intravenous administration of iron dextran, sodium ferric gluconate, and sucrose in patients undergoing hemodialysis. *Pharmacotherapy*. 2007;27:343–350.
44. Geisser P, Baer M, Schaub E. Structure/histotoxicity relationship of parenteral iron preparations. *Arzneimittelforschung*. 1992;42:1439–1452.
45. Ternes N, Scheiber-Mojdehkar B, Landgraf G, Goldenberg H, Sturm B. Iron availability and complex stability of iron hydroxyethyl starch and iron dextran a comparative in vitro study with liver cells and macrophages. *Nephrol Dial Transplant*. 2007;22:2824–2830.
46. Johnson AC, Becker K, Zager RA. Parenteral iron formulations differentially affect MCP-1, HO-1, and NGAL gene expression and renal responses to injury. *Am J Physiol Renal Physiol*. 2010;299:F426–F435.
47. Toblli JE, Cao G, Oliveri L, Angerosa M. Assessment of the extent of oxidative stress induced by intravenous ferumoxytol, ferric carboxymaltose, iron sucrose and iron dextran in a nonclinical model. *Arzneimittelforschung*. 2011;6:399–410.
48. Agarwal R, Leehey DJ, Olsen SM, Dahl NV. Proteinuria induced by parenteral iron in chronic kidney disease – a comparative randomized controlled trial. *Clin J Am Soc Nephrol*. 2011;6:114–121.
49. Weissleder R, Stark DD, Engelstad BL, et al. Supermagnetic iron oxide: pharmacokinetics and toxicity. *AJR Am J Roentgenol*. 1989;152:167–173.
50. Tsuchiya K, Nitta N, Sonoda A, et al. Histological study of the biodynamics of iron oxide nanoparticles with different diameters. *Int J Nanomedicine*. 2011;6:1587–1594.
51. Funk F, Ryle P, Canclini C, Neiser S, Geisser P. The new generation intravenous iron: chemistry, pharmacology, and toxicology of ferric carboxymaltose. *Arzneimittelforschung*. 2010;60:345–353.

Journal of Blood Medicine Dovepress

Publish your work in this journal

The Journal of Blood Medicine is an international, peer-reviewed, open access, online journal publishing laboratory, experimental and clinical aspects of all topics pertaining to blood based medicine including but not limited to: Transfusion Medicine; Blood collection, Donor issues, Transmittable diseases, and Blood banking logistics; Immunohematology; Artificial and alternative blood based therapeutics; Hematology; Biotechnology/nanotechnology of blood related medicine; Legal aspects of blood medicine; Historical perspectives. The manuscript management system is completely online and includes a very quick and fair peer-review system. Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Submit your manuscript here: http://www.dovepress.com/Journal-of-blood-medicine-journal