ADIS DRUG EVALUATION

Ferric Carboxymaltose: A Review of Its Use in Iron Deficiency

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Abstract   Ferric carboxymaltose (Ferinject®, Injectafer®) is an intravenous iron preparation approved in numerous countries for the treatment of iron deficiency. A single high dose of ferric carboxymaltose (up to 750 mg of iron in the US and 1,000 mg of iron in the EU) can be infused in a short time frame (15 min). Consequently, fewer doses of ferric carboxymaltose may be needed to replenish iron stores compared with some other intravenous iron preparations (e.g. iron sucrose). Ferric carboxymaltose improved self-reported patient global assessment, New York Heart Association functional class and exercise capacity in patients with chronic heart failure and iron deficiency in two randomized, placebo-controlled trials (FAIR-HF and CONFIRM-HF). In other randomized controlled trials, ferric carboxymaltose replenished iron stores and corrected anaemia in various populations with iron-deficiency anae-mia, including patients with chronic kidney disease, inflammatory bowel disease or heavy uterine bleeding, postpartum iron-deficiency anaemia and perioperative anaemia. Intravenous ferric carboxymaltose was generally well tolerated, with a low risk of hypersensitivity reactions.

It was generally better tolerated than oral ferrous sulfate, mainly reflecting a lower incidence of gastrointestinal adverse effects. The most common laboratory abnormality seen in ferric carboxymaltose recipients was transient, asymptomatic hypophosphataemia. The higher acquisition cost of ferric carboxymaltose appeared to be offset by lower costs for other items, with the potential for cost savings. In conclusion, ferric carboxymaltose is an important option for the treatment of iron deficiency.

Ferric carboxymaltose in iron deficiency: a summary
A single high dose of ferric carboxymaltose can be infused in a short time frame (15 min), rapidly replenishing iron stores
Compared with some other intravenous preparations, fewer doses may be needed to replenish iron stores
Showed improvement in self-reported patient global assessment, New York Heart Association functional class and exercise capacity in chronic heart failure and iron deficiency
Replenished iron stores and corrected anaemia in various populations with iron-deficiency anaemia
Generally well tolerated, with a low risk of hypersensitivity reactions, and better tolerated than oral ferrous sulfate
Associated with transient, asymptomatic hypophosphataemia
Potential for cost savings

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1 Introduction

Globally, iron deficiency is the most commonly occurring nutritional deficiency and the most common cause of anaemia [1, 2]. Iron deficiency is a common feature of various chronic diseases [e.g. chronic heart failure (CHF), chronic kidney disease] and its aetiology is often multifactorial [3]. Iron deficiency may be associated with poor nutrition, increased utilization of iron (e.g. during pregnancy), blood loss [e.g. heavy uterine bleeding, blood loss associated with gastrointestinal (GI) disorders, surgical blood loss], chronic inflammation or impaired iron absorption [e.g. in inflammatory bowel disease (IBD)] [3–5]. Although particularly prevalent in developing countries, anaemia remains a significant problem in developed countries [2, 5]. Diagnostic criteria for anaemia vary between studies [3], although WHO defines anaemia as a haemoglobin level of <130 g/L in men, <120 g/L in non-pregnant women and <110 g/L in pregnant women [2].

Iron metabolism is a complex process and the 25-amino acid peptide hepcidin is the key regulator of iron homeostasis [6]. Hepcidin is upregulated in chronic inflammation (as seen in cancer or autoimmune conditions), which contributes to the development of anaemia of chronic disease [6]. Other factors affecting the regulation of hepcidin include iron availability, erythropoiesis and hypoxia [6].

Iron deficiency may be absolute or functional [7]. Absolute iron deficiency occurs when iron stores are so low that no iron is available for the production of haemoglobin [7]. The negative iron balance compromises erythropoiesis resulting in iron-deficiency anaemia [4, 8]. In functional iron deficiency, body iron stores are normal or increased, but there is a failure of these stores to release iron rapidly enough to support the demands of the bone marrow [3, 7].

Iron supplementation is used to correct anaemia and replenish iron stores in patients with iron-deficiency anaemia [3]. Ferric carboxymaltose (Ferinject®, Injectafer®) is an intravenous iron preparation approved in numerous countries for the treatment of iron deficiency.

This article reviews the clinical efficacy, tolerability and safety of ferric carboxymaltose in iron deficiency, as well as summarizing its pharmacological properties and results of pharmacoeconomic analyses. Throughout this article, the dose of ferric carboxymaltose and other iron preparations is expressed in milligrams of iron.

2 Pharmacodynamic Properties

The pharmacodynamic properties of ferric carboxymaltose have been reviewed previously [9]; this section provides a brief overview.

Ferric carboxymaltose is formulated as a colloidal solution of polynuclear iron(III) oxyhydroxide stabilized by the carbohydrate polymer carboxymaltose [10, 11]. The ferric carboxymaltose solution has isotonic osmolarity and a pH of 4.5–7.0 and the complex has a molecular mass of ≈ 150 kDa [10–12]. Ferric carboxymaltose is designed to provide controlled delivery of iron to the macrophages of the reticuloendothelial system in the liver, spleen and bone marrow, with subsequent delivery to the transport protein transferrin, without large amounts of ionic iron being released into the serum [10, 11].

The stability of the ferric carboxymaltose complex permits the administration of high doses of iron [11]. In mice, the 50 % lethal dose (LD_{50}) of intravenous ferric carboxymaltose was >1,000 mg iron/kg bodyweight [10], compared with LD_{50} values of 230 mg iron/kg for oral iron sulfate, >200 mg iron/kg for intravenous iron sucrose and >2,500 mg iron/kg for intravenous iron dextran [13].

In patients with anaemia receiving radiolabelled ferric carboxymaltose, maximum red cell uptake of ^{59}Fe of 61–99 % was seen after 16–24 days [14]. Intravenous ferric carboxymaltose transiently increased total serum iron concentrations (see Sect. 3) [15]. Results of clinical trials demonstrating the beneficial effects of ferric carboxymaltose on haemoglobin levels, serum ferritin levels and transferrin saturation are discussed in Sect. 4.

Ferric carboxymaltose was associated with transient, asymptomatic hypophosphataemia in patients with iron deficiency (see Sect. 5). The mechanisms underlying this hypophosphataemia are unclear, although one possible mechanism is an effect on the phosphate-regulating peptide hormone fibroblast growth factor 23 (FGF23). In women with heavy uterine bleeding and iron-deficiency anaemia, serum levels of intact FGF23 increased from baseline to a significantly ($p < 0.05$) greater extent with intravenous ferric carboxymaltose than with intravenous iron dextran, with no significant between-group difference in the change from baseline in plasma levels of C-terminal FGF23 [16]. The transient increase in intact FGF23 was accompanied by a transient reduction in serum phosphate levels [16].

Ferric carboxymaltose lowered elevated platelet counts and normalized platelet activation in patients with IBD [17, 18]. For example, in patients with IBD and secondary thrombocytosis in the ThromboVIT trial, mean platelet counts were significantly ($p < 0.01$) lower at week 6 in patients receiving ferric carboxymaltose 500–1,500 mg than in placebo recipients, although there was no significant difference in the proportion of ferric carboxymaltose versus placebo recipients achieving a reduction in platelet count of ≥ 25 % [18]. Significant ($p < 0.05$) reductions from baseline in platelet activation were also seen with ferric carboxymaltose [18].

Prolonged exposure to high levels of non-transferrin bound iron (as seen in untreated patients with iron overload disorders) may trigger oxidative stress in organs such as the liver, heart and pancreas [19]. Thus, there has been concern that iron compounds that release large amounts of ionic iron into the circulation may potentiate oxidative stress [20, 21]. However, ferric carboxymaltose appears to be associated with a relatively low risk of oxidative stress, reflecting the fact that iron is predominantly deposited in the reticuloendothelial system [10, 11]. For example, significant ($p < 0.01$) increases in oxidative stress and pro-inflammatory markers were seen in the liver, heart and kidneys of rats administered low-molecular-weight (LMW) or high-molecular-weight (HMW) iron dextran or sodium ferric gluconate (ferrous gluconate), compared with rats administered ferric carboxymaltose or iron sucrose [22]. In addition, ferric carboxymaltose had no effect on plasma levels of intercellular adhesion molecule (ICAM) or vascular adhesion molecule or proinflammatory markers in patients with nondialysis-dependent chronic kidney disease [23].

However, reactive oxygen species production, ICAM-1 expression and apoptosis were significantly ($p < 0.005$ vs. control) increased from baseline when mononuclear cells from haemodialysis patients or healthy volunteers were cultured in vitro with ferric carboxymaltose, iron sucrose, iron dextran or sodium ferric gluconate, with significantly ($p < 0.005$) greater effects seen in mononuclear cells from haemodialysis patients than in mononuclear cells from healthy volunteers [20].

Baseline levels of erythrocyte glutathione peroxidase (eGPx) (an antioxidant enzyme) were significantly ($p = 0.01$) higher among patients with nondialysis-dependent chronic kidney disease and iron-deficiency anaemia who responded to a single dose of ferric carboxymaltose 1,000 mg than in nonresponders [24]. Multivariate analysis revealed that eGPx levels independently predicted response to ferric carboxymaltose [24].

3 Pharmacokinetic Properties

Total serum iron concentrations increased rapidly following the intravenous administration of single ferric carboxymaltose doses of 100, 500, 800 or 1,000 mg of iron to patients with mild iron-deficiency anaemia; the 100 mg dose was administered as an intravenous bolus and the 500, 800 and 1,000 mg doses were administered as 15-min intravenous infusions [15]. Following single doses of ferric carboxymaltose 100, 500, 800 and 1,000 mg, geometric mean maximum serum iron concentrations of 37, 156, 319 and 331 μg/mL, respectively, were reached in a mean time of 0.3, 0.3, 1.0 and 1.2 h, respectively [15]. The geometric

mean area under the serum concentration-time curve (AUC) from time zero to 24 h was 333 μg·h/mL with ferric carboxymaltose 100 mg, and the AUC from time zero to 72 h was 2,345, 5,171 and 6,277 μg·h/mL with ferric carboxymaltose 500, 800 and 1,000 mg, respectively [15]. Repeated administration of ferric carboxymaltose 500 or 1,000 mg did not result in accumulation of iron in serum [25].

The iron in ferric carboxymaltose had a volume of distribution of ≈ 3 L [15, 26]. Ferric carboxymaltose did not cross the placenta in an in vitro perfusion model [27].

The iron in ferric carboxymaltose was rapidly cleared from plasma [26], with positron emission tomography demonstrating that the major portion of a radiolabelled injected iron dose was distributed to the bone marrow, with uptake also seen in the liver and spleen [14]. Following single doses of ferric carboxymaltose 100–1,000 mg, geometric mean clearance was 2.6–4.3 mL/min [15]. In vitro experiments showed that the carbohydrate moiety underwent hydrolysis to oligoglucose units (e.g. maltotriose, maltose and glucose) [11].

Renal elimination of iron following administration of ferric carboxymaltose was negligible [26, 28]. Following single doses of ferric carboxymaltose 100–1,000 mg, the geometric mean terminal elimination half-life was 7.4–12.1 h and the geometric mean residence time was 11.2–16.6 h [15].

When intravenous ferric carboxymaltose was administered to women with postpartum iron-deficiency anaemia, mean iron concentrations in breast milk increased from 0.500 mg iron/kg breast milk at baseline to a maximum 1.447 mg/kg at 24-h postdose [29]. Neither mother nor infants had evidence of adverse events associated with the administration of ferric carboxymaltose to breast-feeding mothers [29].

4 Therapeutic Efficacy in Iron Deficiency

The main focus of this section is the results of randomized controlled trials examining the efficacy of ferric carboxymaltose in iron deficiency. Where relevant, results of studies in real-world settings are also briefly discussed, with a focus on prospective data.

4.1 In Chronic Heart Failure

The efficacy of ferric carboxymaltose in patients with CHF and iron deficiency (with or without anaemia) was examined in the randomized, double-blind, placebo-controlled, multinational FAIR-HF [30] and CONFIRM-HF [31] trials. The trials were of 26 [30] or 52 [31] weeks' duration.

Inclusion criteria included New York Heart Association (NYHA) class II or III CHF [30, 31], left ventricular

ejection fraction (LVEF) of ≤40 % (for NYHA class II patients) or ≤45 % (for NYHA class III patients) [30] or ≤45 % [31], a haemoglobin level of 95–135 g/L [30] or <150 g/L [31], iron deficiency (i.e. serum ferritin level of <100 ng/mL, or 100–299 ng/mL with a transferrin saturation of <20 %) [30, 31] and elevated natriuretic peptide levels (brain natriuretic peptide level of >100 pg/mL and/or N-terminal-pro-brain natriuretic peptide level of >400 pg/mL) [31].

In FAIR-HF, patients received intravenous ferric carboxymaltose 200 mg once weekly until iron repletion was achieved (calculated total iron requirement based on the Ganzoni formula) and then every 4 weeks during the maintenance phase; the maintenance phase started at week 8 or 12, depending on the iron repletion dose [30]. In CONFIRM-HF, patients received ferric carboxymaltose at baseline and, if necessary, at week 6 to correct iron deficiency (cumulative dose of 500–2,000 mg with the dose based on bodyweight and haemoglobin levels), followed by maintenance doses of 500 mg at weeks 12, 24 and 36 if iron deficiency was still present [31].

Among ferric carboxymaltose and placebo recipients at baseline, 17.4 versus 18.7 % in FAIR-HF [30] and 53.3 versus 60.3 % in CONFIRM-HF [31] were NYHA class II, 82.6 versus 81.3 % [30] and 46.7 versus 39.7 % [31] were NYHA class III, mean LVEF was 31.9 versus 33.0 % [30] and 37.1 versus 36.5 % [31], mean haemoglobin was 119 versus 119 g/L [30] and 124 versus 124 g/L [31], mean serum ferritin was 53 versus 60 ng/mL [30] and 57 versus 57 ng/mL [31] and mean transferrin saturation was 17.7 versus 16.7 % [30] and 20.2 versus 18.2 % [31].

The primary endpoints were self-reported patient global assessment and NYHA functional class at week 24 [30] and the change in 6-min walk test distance from baseline to week 24 [31]. Efficacy was assessed in the full analysis set [30, 31].

4.1.1 FAIR-HF Trial

Ferric carboxymaltose was beneficial in patients with CHF and iron deficiency with or without anaemia [30]. The odds ratios (ORs) for improvements in self-reported patient global assessment and NYHA functional class both significantly favoured ferric carboxymaltose versus placebo recipients at 24 weeks (Table 1). At week 24, 50 % of ferric carboxymaltose recipients and 28 % of placebo recipients reported much or moderate improvement (based on self-reported patient global assessment), and 47 % of ferric carboxymaltose recipients and 30 % of placebo recipients were NYHA class I or II [30]. ORs for both improvement in self-reported patient global assessment and NYHA functional class also significantly ($p < 0.001$)

favoured ferric carboxymaltose versus placebo recipients at weeks 4 and 12 [30].

Ferric carboxymaltose had a consistent treatment effect in patients with anaemia (haemoglobin level ≤120 g/L) and in those without anaemia [32]. ORs for improved self-reported patient global assessment were 2.48 (95 % CI 1.49–4.14; $p < 0.001$) in patients with anaemia and 2.60 (95 % CI 1.55–4.35; $p < 0.001$) in patients without anaemia, and ORs for improvement by one NYHA functional class were 1.90 (95 % CI 1.06–3.40; $p = 0.03$) in patients with anaemia and 3.39 (95 % CI 1.70–6.75; $p < 0.001$) in patients without anaemia [32]. It should be noted that haemoglobin levels at week 24 were significantly ($p < 0.001$) higher in ferric carboxymaltose than in placebo recipients in the overall population and in the subgroup of patients with anaemia at baseline, with no significant between-group difference in the subgroup of patients without anaemia at baseline [30].

The mean distance achieved on the 6-min walk test was significantly ($p < 0.001$) longer with ferric carboxymaltose than with placebo at weeks 4 (294 vs. 269 m), 12 (312 vs. 272 m) and 24 (313 vs. 277 m) (mean baseline values were 274 vs. 269 m) [30]. At week 24, the increase in 6-min walk distance was significantly correlated with a reduction in red cell distribution width ($r = -0.25$; $p < 0.0001$), according to results of a post hoc analysis [33]. Although red cell distribution width initially increased in ferric carboxymaltose recipients, it was significantly ($p < 0.05$) lower with ferric carboxymaltose than with placebo at week 24 [33].

Ferric carboxymaltose improved health-related quality of life (HR-QOL) in patients with CHF and iron deficiency [34]. The mean changes from baseline in European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS) scores significantly ($p < 0.001$) favoured ferric carboxymaltose versus placebo recipients at weeks 4 (6.0 vs. 0.8), 12 (7.9 vs. 2.4) and 24 (9.1 vs. 3.4) (mean baseline values were 54 in both treatment groups), as did the mean changes from baseline in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary scores at weeks 4 (9.4 vs. 3.5), 12 (12.2 vs. 4.6) and 24 (12.8 vs. 6.2) (mean baseline values were 52 and 53). Ferric carboxymaltose improved HR-QOL in patients with and without anaemia [34]. Multivariate analysis showed that intravenous iron therapy, lower NYHA class and better 6-min walk test results were associated with higher HR-QOL, whereas a history of stroke and reduced renal function were associated with lower HR-QOL [35].

Ferric carboxymaltose improved renal function in iron-deficient patients with CHF, according to an additional analysis of FAIR-HF (available as a poster) [36]. At week 24, the change from baseline in estimated glomerular filtration rate significantly favoured ferric carboxymaltose

Table 1 Efficacy of ferric carboxymaltose in patients with chronic heart failure and iron deficiency. Shown are the primary endpoints in the randomized, double-blind, multinational FAIR-HF [30] and CONFIRM-HF [31] trials

Study (study name)	Endpoint	FCM	PL
Anker et al. [30, 125] (FAIR-HF)	Self-reported patient global assessment at 24 weeks[a]		
	Much improved (% of pts)	16	10
	Moderately improved (% of pts)	34	17
	A little improved (% of pts)	26	28
	Unchanged (% of pts)	18	35
	A little, moderately or much worse (% of pts)	3	7
	Dead (% of pts)	2	3
	Odds ratio for improvement (95 % CI)	2.51 (1.75–3.61)**	
	NYHA functional class at 24 weeks[b]		
	Class I (% of pts)	6	1
	Class II (% of pts)	41	29
	Class III (% of pts)	50	65
	Class IV (% of pts)	1	3
	Dead (% of pts)	2	3
	Odds ratio for improvement by one class (95 % CI)	2.40 (1.55–3.71)**	
Ponikowski et al. [31, 126] (CONFIRM-HF)	LSM change from baseline to week 24 in 6MWT distance[c] (m) [mean baseline value; m]	+18* [288]	−16 [302]

6MWT 6-min walk test, *FCM* ferric carboxymaltose, *LSM* least squares mean, *NYHA* New York Heart Association, *PL* placebo, *pts* patients

* $p < 0.01$, ** $p < 0.001$ vs. PL

[a] 292 FCM recipients and 149 PL recipients were evaluable for self-reported patient global assessment

[b] 294 FCM recipients and 150 PL recipients were evaluable for NYHA functional class

[c] 150 FCM recipients and 151 PL recipients were in the full analysis set

versus placebo recipients (between-group difference 4.0 mL/min/1.73 m^2; $p = 0.017$) [36].

4.1.2 CONFIRM-HF Trial

A significant improvement from baseline to week 24 in the 6-min walk test distance was seen with ferric carboxymaltose versus placebo in patients with CHF and iron deficiency in the CONFIRM-HF trial (Table 1), with a least squares mean between-group difference of 33 m ($p = 0.002$) [31]. The improvement in 6-min walk test distance was maintained at later time points; the difference between ferric carboxymaltose and placebo recipients was +42 m at week 36 and +36 m at week 52 (both $p < 0.001$). No significant interaction was seen in terms of the treatment effect in patients with anaemia (haemoglobin <120 g/L) or without anaemia (haemoglobin ≥120 g/L) (p-value for interaction 0.15) [31].

Ferric carboxymaltose recipients were significantly ($p < 0.05$) more likely than placebo recipients to have improvements in self-reported patient global assessment at weeks 12, 24, 36 and 52 and in NYHA class at weeks 24, 36 and 52 [31]. Significant ($p < 0.05$) improvements were seen with ferric carboxymaltose versus placebo in terms of the least squares mean change in fatigue scores at weeks

12, 24, 36 and 52 and for KCCQ scores at weeks 12, 36 and 52. A significant ($p = 0.002$) between-group difference favouring ferric carboxymaltose was seen for the least squares mean change in EQ-5D VAS score at week 36, with no significant between-group difference seen at other time points [31].

Between-group differences significantly ($p < 0.001$) favoured ferric carboxymaltose versus placebo recipients in terms of ferritin levels at week 24 (265 ng/mL) and week 52 (200 ng/mL), transferrin saturation at week 24 (8.9 %) and week 52 (5.7 %) and haemoglobin levels at week 24 (6 g/L) and week 52 (10 g/L) [31].

4.2 In Chronic Kidney Disease

Several randomized, open-label, multicentre trials examined the efficacy of intravenous ferric carboxymaltose in patients with chronic kidney disease and iron-deficiency anaemia [37–41]. Patients had nondialysis-dependent chronic kidney disease [37–39, 41] and/or were undergoing haemodialysis [40, 41]. Patients with nondialysis-dependent chronic kidney disease had haemoglobin levels of ≤110 g/L [39] or ≤115 g/L [37, 41] or at least one haemoglobin value of 90–110 g/L within 4 weeks of randomization [38], and a ferritin level of ≤100 ng/mL [37,

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