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REVIEW

Differences between intravenous iron products: focus on treatment of iron deficiency in chronic heart failure patients

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Abstract

Iron deficiency is the leading cause of anaemia and is highly prevalent in patients with chronic heart failure (CHF). Iron deficiency, with or without anaemia, can be corrected with intravenous (i.v.) iron therapy. In heart failure patients, iron status screening, diagnosis, and treatment of iron deficiency with ferric carboxymaltose are recommended by the 2016 European Society of Cardiology guidelines, based on results of two randomized controlled trials in CHF patients with iron deficiency. All i.v. iron complexes consist of a polynuclear Fe(III)-oxyhydroxide/oxide core that is stabilized with a compound-specific carbohydrate, which strongly influences their physico-chemical properties (e.g. molecular weight distribution, complex stability, and labile iron content). Thus, the carbohydrate determines the metabolic fate of the complex, affecting its pharmacokinetic/pharmacodynamic profile and interactions with the innate immune system. Accordingly, i.v. iron products belong to the new class of non-biological complex drugs for which regulatory authorities recognized the need for more detailed characterization by orthogonal methods, particularly when assessing generic/follow-on products. Evaluation of published clinical and non-clinical studies with different i.v. iron products in this review suggests that study results obtained with one i.v. iron product should not be assumed to be equivalent to other i.v. iron products that lack comparable study data in CHF. Without head-to-head clinical studies proving the therapeutic equivalence of other i.v. iron products with ferric carboxymaltose, in the highly vulnerable population of heart failure patients, extrapolation of results and substitution with a different i.v. iron product is not recommended.

Keywords Iron deficiency; Intravenous; Parenteral; Nanomedicines; Heart failure; Ferric carboxymaltose

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Introduction

Iron deficiency (ID) is a common condition and the leading cause of anaemia. The prevalence is high among patients with chronic diseases, including chronic heart failure (CHF), inflammatory bowel disease (IBD), chronic kidney disease (CKD), or cancer, and in women of childbearing age.[1,2] In a CHF cohort of 1506 patients, 50% were identified as iron deficient when applying a frequently used definition of ID that is in line with European, Australian, and US heart failure (HF) guidelines [serum ferritin $<$100 μg/L or serum ferritin 100–299 μg/L and transferrin saturation (TSAT) $<$20%].[3–6] Notably, ID was not only frequent among anaemic patients (61.2%) but also detected in 45.6% of non-anaemic patients. ID is associated with HF symptoms, such as breathlessness, fatigue, reduced exercise capacity, worse functional status [New York Heart Association (NYHA) class], greater risk of hospitalization, and reduced survival in HF patients, and may contribute to muscle dysfunction.[7–9] The medical need for treatment of ID and iron deficiency anaemia (IDA) in these patients is high.[5]

In patients with CHF, both ID and IDA can be corrected with intravenous (i.v.)[10,11] iron therapy. In a 16 week, placebo-controlled, randomized trial of oral iron in patients with CHF, oral iron neither resolved ID nor had any significant effect on exercise capacity measured by peak oxygen consumption (pVO_2) or 6 min walk test (6MWT).[12] Intravenous iron therapy is generally indicated in patients who are unresponsive or intolerant to oral iron or in patients who require rapid correction of ID or IDA.[1,2] Because of better and faster response and better tolerance, i.v. iron therapy is well established and recommended as the preferred treatment in patients with IBD, haemodialysis-dependent CKD, or chemotherapy-induced anaemia.[13–15] Current European Society of Cardiology (ESC) HF guidelines recommend inclusion of serum ferritin and TSAT tests in the initial assessment of newly diagnosed patients.[5] Furthermore, the ESC guidelines specifically recommend treatment with i.v. ferric carboxymaltose (FCM) for symptomatic iron-deficient patients in order to alleviate HF symptoms and improve exercise capacity and quality of life (QoL). This recommendation (Class IIa, Level A) is based on improvements in self-reported patient global assessment (PGA), QoL, and NYHA class (over 6 months) and improvement of functional capacity over 52 weeks in the randomized, controlled trials FAIR-HF and CONFIRM-HF, respectively.[10,11] In addition to these potentially 'subjective' endpoints, the 52 week CONFIRM-HF study also showed a significantly lower rate of hospitalizations due to worsening of HF among FCM-treated vs. placebo-treated patients. In the interim, the evidence base showing the benefits of FCM has broadened[12,16,17] as summarized in this review.

Currently available i.v. iron complexes apart from FCM include iron sucrose (IS), sodium ferric gluconate (SFG), low-molecular-weight iron dextran, ferumoxytol (FMX, withdrawn in the European Union[18]), and iron isomaltoside 1000 (IIM). As a common principle, i.v. iron complexes consist of a polynuclear Fe(III)-oxyhydroxide/oxide core that is stabilized by a compound-specific carbohydrate.[19,20] However, these different carbohydrates also result in substantially differing physico-chemical properties (e.g. molecular weight distribution, complex stability, and labile iron content) and pharmacokinetic/pharmacodynamic profiles (e.g. plasma half-life) (*Table 1*) of the different i.v. iron complexes.[2,20,21] Based on the chemical identity of the carbohydrate, i.v. iron complexes can be classified as non-dextran-based and dextran/dextran-based complexes. Dextran or dextran-based complexes are very stable with low labile iron content independent of their molecular weight.[20,23,24] For non-dextran-based complexes, stability correlates with molecular weight; that is, complexes with higher molecular weight are more stable and contain less labile iron than complexes with lower molecular weight.[20,24] The differences in properties of i.v. iron complexes are reflected in the various approved maximum single doses and administration rates for different products.[1,25,26]

Table 1 Overview of characteristics of i.v. iron products

Active ingredient	Sodium ferric gluconate	Iron sucrose	Ferric carboxymaltose	Ferumoxytol	Iron isomaltoside 1000	LMW iron dextran
Brand name	Ferrlecit®	Venofer®	Ferinject® Injectafer®	Feraheme® Rienso®[a]	Monofer®	Cosmofer® INFeD®
Carbohydrate	Gluconate	Sucrose	Carboxymaltose	Polyglucose sorbitol carboxymethyl ether	Isomaltoside 1000[b]	Dextran
Weight average molecular weight (kDa)[20]	37 500	43 300	150 000	185 000	69 000	103 000
Stability	Low	Medium	High	High	High	High
Labile iron content (%)[24]	3.2	3.5	0.5	N/A	1	2
In vitro reactivity with anti-dextran antibodies[54]	No	No	No	Yes	Yes	Yes
Plasma terminal half-life (h)[20] [iron dose (mg)]	1.42 (125)	5.3 (100)	7.4/9.4 (100/1000)	14.7 (316)	20.8/22.5 (100/200)	27–30 (500–2000)
Max single iron dose (mg) [min admin time (min)][c]	125 (10–60)	200 (10–30)	1000 (15)	510 (15)	20 mg/kg BW (15–30)	20 mg/kg BW (4–6 h)

BW, body weight; i.v., intravenous; LMW, low molecular weight; N/A, not applicable.
[a]The marketing authorization of Rienso® was withdrawn by the European Commission at the request of the manufacturer on 13 April 2015.[16]
[b]In the German SPC (Medice Pharma GmbH & Co. KG, Iserlohn, Germany 2011); iron citrate isomaltooligosaccharide alcohol-hydrate complex.
[c]Most common maximal dose and corresponding minimal administration time. The exact posology may vary between markets; see local prescribing information.

The aim of this review was to assess whether the substantial amount of data supporting clinical efficacy of FCM in CHF patients can be taken as reference for other i.v. iron products that lack comparable study data. Published clinical and non-clinical comparisons of different i.v. iron products were assessed to address the following questions:

(i) Are there differences in the clinical safety/tolerability and efficacy between the i.v. iron products?
(ii) How do the differences in the physico-chemical properties of the i.v. iron complexes affect the clinical outcome?
(iii) Are differences between i.v. iron products acknowledged by authorities?
(iv) Should the interchangeability of the products be restricted or can study results with one i.v. iron product be translated to other i.v. iron products lacking comparable data?

Efficacy and tolerability of ferric carboxymaltose in chronic heart failure patients

In the FAIR-HF study,[10] a greater proportion of patients in the FCM group achieved a 'much or moderately' improved PGA score and an improved NYHA functional class compared with placebo-treated patients after 24 weeks (*Table 2* and *Figure 1*). Significantly, better outcomes with FCM treatment were also observed in the 6MWT and health-related quality of life (HRQoL) after 6 months of treatment. Moreover, patients treated with FCM experienced cardiac events less frequently and required fewer hospitalizations than placebo-treated patients. Similar rates of adverse events (AEs) and deaths between treatment groups indicate that i.v. FCM treatment is well tolerated in this vulnerable patient population. Several post hoc analyses showed significant increases in HRQoL scores in the FCM group from Week 4 onwards[28]; a positive effect of improved functional capacity (6MWT) on HRQoL[27]; benefit of ID correction even in the absence of anaemia[29]; reassuring safety of FCM in CHF patients with renal impairment[30]; and cost-effectiveness in different countries.[31–33]

CONFIRM-HF[11] expanded the validity of the favourable outcomes with FCM to a more general CHF patient population (i.e. more patients with lower NYHA class) and for a longer follow-up period (i.e. 52 vs. 24 weeks). FCM-treated patients showed significantly greater improvements in the primary endpoint 6MWT from baseline to Weeks 24 and 52 compared with patients in the placebo group (*Table 2*). The favourable treatment effect was seen across all pre-specified subgroups including patients with and without anaemia. Additionally, statistically significant benefits in FCM-treated patients were seen in PGA score (*Figure 1*), fatigue score, and Kansas City Cardiomyopathy Questionnaire score from Week 12 onwards, in NYHA class from Week 24 onwards, and European Quality of Life-5 Dimensions score from Week 36 onwards. Furthermore, there was a significant reduction in the risk of hospitalization due to worsening of CHF. The AE rates and deaths were similar between treatment groups.

EFFECT-HF,[17] investigating the effects of FCM on exercise capacity (primary endpoint pVO_2) in patients with ID and CHF, showed a significant benefit in pVO_2 among FCM vs. standard-of-care-treated patients after 24 weeks (1.04 ± 0.44 mL/kg/min difference in pVO_2 between groups) (*Table 2*). Also, iron parameters (TSAT and serum ferritin) and haemoglobin (Hb) showed a significantly greater improvement in the FCM vs. the standard-of-care group. Adjustment for patients with or without anaemia at baseline showed no significant interaction.

A meta-analysis of individual patient data from four randomized, placebo-controlled trials[16] evaluated data from 839 patients with systolic HF and ID. FCM-treated patients (504) showed significantly lower rates of the composites of recurrent cardiovascular (CV)-related hospitalizations and mortality (rate ratio 0.59; $P = 0.009$), recurrent HF hospitalizations and CV mortality (rate ratio 0.53; $P = 0.011$), and recurrent CV hospitalizations and all-cause mortality (rate ratio 0.60; $P = 0.009$). AE incidence rates were similar in the FCM and placebo groups (105.4 vs. 95.8 per 100 patient-years). AE-related withdrawals occurred less frequently in the FCM groups (6.3% vs. 10.1%). No serious or severe hypersensitivity reactions (HSRs) were reported.

The clinical efficacy of FCM in CHF patients was also assessed in a retrospective observational study.[34] Among 70 iron-deficient, FCM-treated patients with NYHA Class II or III (44.3% Class II) CHF, iron parameters significantly improved 3 months post FCM treatment vs. baseline. FCM infusions were well tolerated, and no complications, including allergic reactions, occurred.

Other trials investigating i.v. iron, particularly FCM, in acute HF, asymptomatic and advanced CHF, and HF with preserved ejection fraction [AFFIRM-AHF (NCT02937454) and FAIR-HFpEF (NCT03074591)] and repeated doses over a ≥1 year follow-up interval [AFFIRM-AHF (NCT02937454), HEART-FID (NCT03037931), FAIR-HF2 (NCT03036462), and IRONMAN (NCT02642562)] are ongoing. An illustrative algorithm for the correction of ID in patients with HF has been recently published.[35]

Efficacy and tolerability of other intravenous iron products in chronic heart failure patients

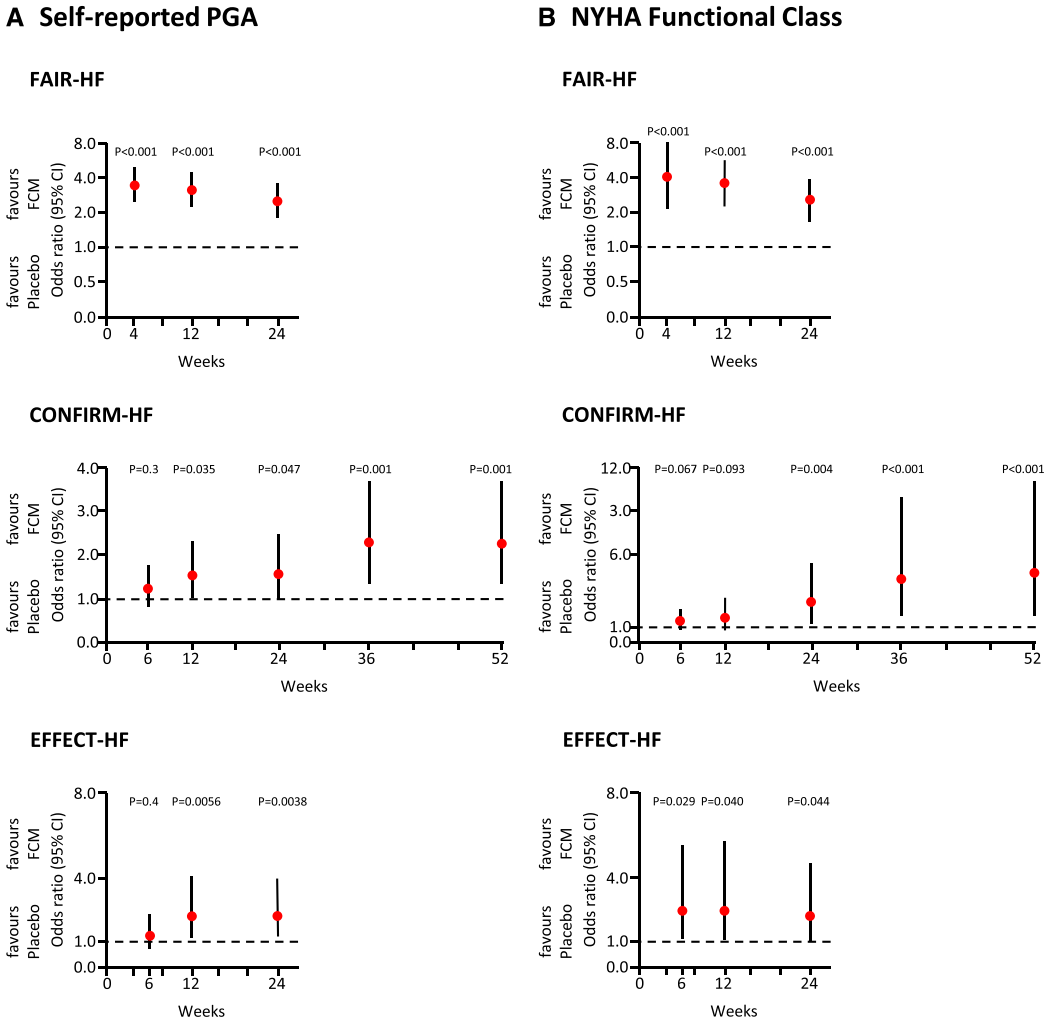
Two small placebo-controlled studies investigated i.v. IS in iron-deficient CHF patients and showed improvement of haematological parameters as well as QoL and NYHA scores

Table 2 Design and key outcomes of randomized controlled trials of FCM in heart failure patients

	FAIR-HF[10]	CONFIRM-HF[11]	EFFECT-HF[17]
CHF patient population (all ambulatory patients)	NYHA Class II or III (17.4% Class II in FCM), LVEF ≤ 40% or ≤ 45%, Hb 9.5 to 13.5 g/dL	NYHA Class II or III (53.3% Class II in FCM), LVEF ≤ 45%, Hb < 15.0 g/dL SF < 100 μg/L or SF 100–299 μg/L and TSAT < 20%	NYHA Class II or III (53.3% Class II in FCM), LVEF ≤ 45%, Hb < 15.0 g/dL
Groups (*n*)[a]	FCM (304) Placebo (155)	FCM (150) Placebo (151)	FCM (86) SoC (86)
Duration (weeks)	24	52	24
Total dose calculation	Ganzoni	Baseline Hb, BW	Baseline Hb, BW
Iron dosing schedule	Correction: 200 or 100 mg qwk Maintenance: 200 mg q4wk	Correction: 500 or 1000 mg q6wk Maintenance (if ID present): 500 mg q12wk	Correction: 500 or 1000 mg q6wk Maintenance (if ID present): 500 mg Week 12
Primary endpoint(s)	PGA at Week 24 and change in NYHA baseline to Week 24 PGA: 50% vs. 28% reported much or moderate improvement (OR 2.51; 95% CI 1.75–3.61; $P < 0.001$) NYHA: 47% vs. 30% achieving NYHA Class I or II (OR for improvement by one class, 2.40; 95% CI, 1.55–3.71; $P < 0.001$)	Change in 6MWT baseline to Week 24 6MWT [m]: increase by 18 ± 8 vs. decrease by 16 ± 8 (difference 33 ± 11; $P = 0.002$)	Change in weight-adjusted pVO_2 baseline to Week 24 pVO_2 [mL/kg/min]: decrease of 0.2 vs. 1.2 (significant difference of 1.04; $P = 0.02$)
Selected secondary endpoints	At Week 24 6MWT [m]: 313 ± 7 vs. 277 ± 10 (difference 35 ± 8; $P < 0.001$) EQ-5D: 63 ± 1 vs. 57 ± 2 (difference 7 ± 2; $P < 0.001$)	PGA: significant benefit as of Week 12 [$P = 0.035$ (Week 12) and $P = 0.001$ (Week 52)] NYHA: significant benefit as of Week 24 [$P = 0.004$ (Week 24) and $P = 0.001$ (Week 52)] 6MWT [m]: at Week 52, +14 vs. −22 ($P < 0.001$) EQ-5D: significant benefit at Week 36 ($P = 0.002$), numerical benefit at Week 52 ($P = 0.12$)	PGA: significant benefit at Week 24 ($P = 0.0004$) NYHA: significant benefit at Week 24 onwards ($P = 0.001$)
Iron-related parameters	At Week 24 Hb [g/dL]: 13.0 ± 0.1 vs. 12.5 ± 0.1 ($P < 0.001$) SF [μg/L]: 312 ± 13 vs. 74 ± 8 ($P < 0.001$) TSAT [%]: 29 ± 1 vs. 19 ± 1 ($P < 0.001$)	At Week 52 (baseline adjusted treatment effect FCM vs. placebo) Hb [g/dL]: 1.0 ± 0.2 ($P < 0.001$) SF [μg/L]: 200 ± 19 ($P < 0.001$) TSAT [%]: 5.7 ± 1.2 ($P < 0.001$)	At Week 24 (baseline adjusted treatment effect FCM vs. placebo) Hb [g/dL]: 0.74 ± 0.17 ($P < 0.001$) SF [μg/L]: 189 ± 17 ($P = 0.001$) TSAT [%]: 4.7 ± 1.4 ($P = 0.0007$)
Safety endpoints	Death: 1.6% vs. 2.6% Death, CV-related: 1.3% vs. 2.6% Hospitalization or death, CV-related: 6.9% vs. 14.3% ($P = 0.14$) Hospitalization or death, due to worsening of HF: 3.9% vs. 8.4% ($P = 0.15$)	Death: 8.0% vs. 9.3% Death, CV-related: 7.3% vs. 7.9% Hospitalization, CV-related: 17.3% vs. 33.8% ($P = 0.097$) Hospitalization, due to worsening of HF: 6.6% vs. 21.2% ($P = 0.009$)	Death: 0% vs. 4.7% Hospitalization, CV-related: 20.5% vs. 10.6% Hospitalization, due to worsening of HF: 12.5% vs. 7.1%

6MWT, 6 min walk test; BW, body weight; CHF, chronic heart failure; CI, confidence interval; CV, cardiovascular; EQ-5D, European Quality of Life-5 Dimensions; FCM, ferric carboxymaltose; Hb, haemoglobin; HF, heart failure; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; OR, odds ratio; PGA, patient global assessment; pVO_2, peak oxygen consumption; qw, weekly; q4wk (q6wk, q12wk) every 4 (6, 12) weeks; SF, serum ferritin; SoC, standard of care; TSAT, transferrin saturation.
[a]In full analysis set.

Figure 1 Self-reported (A) patient global assessment (PGA) and (B) New York Heart Association (NYHA) functional class outcomes are consistently in favour of ferric carboxymaltose (FCM) across randomized, controlled trials (figures reproduced from Anker *et al.*,[10] Ponikowski *et al.*,[11] and van Veldhuisen *et al.*[17]). CI, confidence interval.



(*Table 3*).[36,37] The study FERRIC-HF[36] enrolled anaemic as well as non-anaemic patients, showing a significant treatment effect of IS on pVO_2 for anaemic patients. Notably, improvement in pVO_2 was related to changes in TSAT (n = 18; r = 0.62; P = 0.006) but not to changes in Hb. One study comparing IS vs. oral iron in CHF, IRON-HF,[38] was terminated when only 23 patients were included due to recruitment issues. Despite the lack of statistical power to detect statistically significant differences, a clinically relevant difference of 4.36 mL/kg/min in VO_2 max between the IS group and the oral iron group was found. While ferritin levels increased in both treatment groups, TSAT increased more in the IS group.

In addition, two small single-arm studies using SFG or IIM were reported.[39,40] In the SFG study, 13 patients with NYHA Classes III–IV and IDA were treated with an accelerated i.v. iron regimen, comprising twice daily 2 h infusions of 250 mg iron until the iron deficit was corrected or the patient was discharged.[40] At 1–4 weeks post-treatment, Hb, serum ferritin, and TSAT were significantly increased, and SFG was considered well tolerated in these advanced-stage CHF patients. No QoL assessments were made in this small study. In the second study, 20 patients with CHF and IDA (Hb $<$ 11 g/dL and serum ferritin $<$ 800 μg/L) were treated with IIM as single infusions of 650–1000 mg iron over 50–67 min.[39] There was no significant increase in Hb at Weeks 1, 2, 4, and 8. Haematocrit was significantly increased at Week 8. Mean serum ferritin and TSAT levels increased from 180 μg/L and 22.1% at baseline to 410 μg/L and 28.1% at Week 8, respectively. No treatment-related AEs occurred; however, two patients were withdrawn from the study for unspecified reasons after exposure to IIM. QoL, assessed via linear analogue scale assessment questionnaire, was improved both at 4 and 8 weeks compared with baseline.

Table 3 Design and key outcomes of randomized controlled trials of i.v. iron products other than FCM in heart failure patients

	Toblli[37]	FERRIC-HF[36]	IRON-HF[38]
CHF patient population (all ambulatory patients)	NYHA Classes II to IV LVEF ≤ 35%, CreCl ≤ 90 mL/min Hb < 12.5 g/dL (m) or <11.5 g/dL (f) SF < 100 μg/L and/or TSAT < 20%	NYHA Class II or III LVEF ≤ 45% Hb < 12.5 g/dL (anaemic) or 12.5–14.5 (non-anaemic) SF < 100 μg/L or SF 100–300 μg/L and TSAT < 20%	NYHA Classes II to IV LVEF ≤ 40% Hb 9.0–12.0 g/dL TSAT < 20% and SF < 500 μg/L
Groups (*n*)	IS (20) Placebo (20)	IS (24) Placebo (11) (18 anaemic, 17 non-anaemic patients)	IS (10) Oral iron (7) Placebo (6)
Duration	6 months	18 weeks	3 months[c]
Iron dosing schedule	200 mg qwk for 5 weeks	200 mg qwk until SF ≥ 500 μg/L	IS: 200 mg qwk for 5 weeks Ferrous sulfate: 200 mg TID for 8 weeks
Primary endpoint(s)	Improvement of haematological and renal parameters and change in NT-proBNP level and inflammatory status by C-reactive protein Haematological parameters (see iron-related parameters) CreCl: 39.8 ➔ 44.9 vs. 37.7 ➔ 31.7 NT-proBNP: 256 ➔ 118 vs. 268 ➔ 451 C-reactive protein: 6.1 ➔ 2.3 vs. 6.6 ➔ 6.5 (all $P < 0.01$ for IS vs. placebo and final vs. baseline in IS group)	Change in pVO_2 from baseline to Week 18 pVO_2 [mL/kg/min]: +1.5 ± 2.7 vs. −0.7 ± 1.4 [treatment effect 2.2 (95% CI 0.5–4.0), $P = 0.01$] [in anaemic patients: 3.9 (95% CI 1.1–6.8), $P = 0.009$]	Change in maximum VO_2 from baseline to Month 3 VO_2 max [mL/kg/min]: +3.5 vs. −0.86 vs. +1.86 ($P = 0.399$ over groups[b])
Selected secondary endpoints	Course from baseline to Month 6 NYHA: 2.9 ➔ 2.0 vs. 2.9 ➔ 3.3 6MWT [m]: 192 ➔ 240 vs. 191 ➔ 185 Change in the quality of life (MLHFQ score): 60 ➔ 41 vs. 58 ➔ 59 (all $P < 0.01$ for IS vs. placebo and final vs. baseline in IS group)	Treatment effect from baseline to Week 18 NYHA: −0.6 (−0.9 to −0.2, $P = 0.007$) PGA: 1.7 (95% CI 0.7–2.6, $P = 0.002$) MLHFQ score: −13 (95% CI −26 to 1, $P = 0.07$)	NYHA: Improved in all groups (no further details reported)
Iron-related parameters	Course from baseline to Month 6 Hb [g/dL]: 10.3 ➔ 11.8 vs. 10.2 ➔ 10.3 SF [μg/L]: 73 ➔ 240 vs. 71 ➔ 79 TSAT [%]: 20 ➔ 25 vs. 20 ➔ 20 (all $P < 0.01$ for IS vs. placebo and final vs. baseline in IS group)	Treatment effect from baseline to Week 18 Hb [g/dL]: 0.1 (95% CI −0.8 to 0.9, $P = 0.87$) SF [μg/L]: 273 (95% CI 151–396, $P < 0.001$) TSAT [%]: 11 (95% CI 5–17, $P = 0.001$)	Change from baseline to Month 3 Hb [g/dL]: +1.04 vs. +1.69 vs. +1.1 ($P < 0.001$ vs. baseline, $P = 0.561$ across groups) SF [μg/L]: +126 vs. +103 vs. −42 ($P = 0.368$ vs. baseline, $P = 0.005$ across groups) TSAT [%]: +10 vs. +5 vs. +2 ($P = 0.003$ vs. baseline, $P = 0.018$ across groups)
Safety endpoints	Death: 0 vs. 0 Hospitalizations: 0 vs. 5 [$P < 0.01$, relative risk 2.33 (95% CI 1.59 to 3.42)]	Death: 1[a] vs. 0 Hospitalizations: 12% vs. 27%	Death: 2 vs. 0 vs. 1 (no further details reported)

6MWT, 6 min walk test; CHF, chronic heart failure; CI, confidence interval; CreCl, creatinine clearance; f, female; FCM, ferric carboxymaltose; Hb, haemoglobin; IS, iron sucrose; i.v., intravenous; LVEF, left ventricular ejection fraction; m, male; MLHFQ, Minnesota Living with Heart Failure Questionnaire; NT-proBNP, NT-pro-brain natriuretic peptide; NYHA, New York Heart Association; PGA, patient global assessment; pVO_2, peak oxygen consumption; qwk, weekly; SF, serum ferritin; TID, three times a day; TSAT, transferrin saturation.

[a]Due to intractable cardiac pump failure, unrelated to the study drug.

[b]Most of non-significant results possibly explained by β error due to premature termination of the trial.

[c]Trial discontinued due to recruitment issues.

Clinical differences among intravenous iron products

Differences in efficacy and tolerability between originators and follow-on products

For older i.v. iron products such as IS and SFG, follow-on products are available in many countries and are often substituted at the pharmacy level.[41–43] However, differences in clinical efficacy and tolerability have been reported for follow-on IS products (so-called IS similar, ISSs) that were approved via the abridged generics pathway.

In an observational study in 75 stable haemodialysis patients, a switch from the IS originator (Venofer®, Vifor International Inc., St. Gallen, Switzerland) to an ISS (Mylan SAS, Saint Priest, France, manufactured by Help SA Pharmaceuticals, Athens, Greece) resulted in a significant decrease of mean Hb and TSAT levels (11.5 vs. 11.8 g/dL and 24.5% vs. 49.3%; $P \leq 0.01$) and an increase in iron and erythropoiesis-stimulating agent dose requirements (+34.6% and +13.8%, respectively).[43] Moreover, an increase (+11.9%) in anaemia drug costs was reported. Conversely, a switch from an ISS to the IS originator in 342 stable haemodialysis patients resulted in significant improvements of iron status and reductions of iron and erythropoiesis-stimulating agent dose requirements.[41]

A retrospective study including 658 patients with obstetric or gynaecological conditions, who received the IS originator or an ISS in two different dilutions (ISSd1 and ISSd2) at single doses of 200 mg iron showed significantly more AEs in ISS-treated patients (IS: 1.8%; ISSd1: 11.0%; ISSd2: 14.3%; $P < 0.02$).[42] The most commonly observed AEs were injection site reaction (IS: 1.8%; ISSd1: 6.2%; ISSd2: 8.2%; $P < 0.05$) and phlebitis (IS: 0%; ISSd1: 4.8%; ISSd2: 4.7%; $P < 0.05$). Also, a case report of three ISS-treated patients, who previously tolerated the IS originator well, showed substantial AEs of severe hypovolaemic dysregulation requiring hospitalization, urticaria, oedema, and headache within 1 h after ISS infusion, which had been substituted for the IS originator at the pharmacy level.[44]

Differences in efficacy and tolerability between originator products

No pivotal head-to-head comparisons of different originator i.v. iron products have been conducted in CHF patients, and thus, data on differences in efficacy and safety are limited. Only a few studies in specific patient populations, such as haemodialysis and IBD patients or patients suffering from heavy uterine bleeding, have been published.[22,45–52] However, because most of these studies were conducted with different iron doses, efficacy data cannot be compared. Conversely, notable differences in tolerability have been observed among i.v. iron products, particularly for the risk of HSRs.[53] As the risk of an HSR upon i.v. iron administration is very low, the exact mechanisms have not yet been elucidated. Nevertheless, it is evident that only dextran/dextran-based i.v. iron complexes carry a potential risk for dextran-induced anaphylactic reactions.[54,55]

Hypersensitivity reactions and anaphylactic reactions occurred most frequently with iron dextrans.[56,57] In particular, high-molecular-weight iron dextran is associated with higher HSR rates and more severe reactions, including death.[58,59] A retrospective cohort study of i.v. iron recipients in the US Medicare non-dialysis population showed the highest risk of anaphylaxis for iron dextrans and the lowest risk for IS, but the study could not differentiate between patients who have received high-molecular-weight or low-molecular-weight iron dextran.[57] Serious allergic reactions occurring with the dextran-based FMX recently prompted the US Food and Drug Administration (FDA) to update the label of Feraheme® and add a boxed warning.[60] In the European Union, marketing authorization of Rienso® was withdrawn at the manufacturer's request.[18] However, a recent retrospective, propensity score-matched cohort study (Medicare patients with non-dialysis-dependent CKD or no CKD) showed no significant differences in adverse reactions to FMX and other i.v. iron products (IS, SFG, and iron dextran).[61]

Iron sucrose, a non-dextran-based i.v. iron, was well tolerated, even in patients with a history of intolerance or HSRs to iron dextrans and/or SFG.[62–65] For FCM, another non-dextran i.v. iron, a study in i.v. iron-treated IDA patients (n = 2584) reported HSRs for 0.8% of FCM-treated patients (total iron dose 1500 mg given at varying single doses) compared with 2.4% of patients with standard-of-care i.v. iron, including iron dextran, SFG, and IS.[66] Notably, the approval of the dextran-based IIM has been largely based on preclinical and clinical data of other iron dextrans.[67] A report of IIM investigators suggesting lower HSR rates for IIM vs. IS or FCM is based on non-adjusted cross trial comparisons.[68]

Why are intravenous iron products different from other medicinal products and how does this affect their metabolism?

Intravenous iron complexes have been engineered to allow administration of high doses of iron in relatively short time. Thus, i.v. iron complexes must be stable, non-reactive, and non-toxic. These features are achieved with carbohydrate-

stabilized polynuclear Fe(III)-oxyhydroxide/oxide nanoparticles formulated as colloidal solutions. Accordingly, i.v. iron complexes are polymers and not small molecules as most pharmaceuticals and comprise mixtures of similar but not identical macromolecules. Therefore, they belong to the class of non-biological complex drugs (NBCDs) (*Figure 2*).[69–71] The key attributes of an NBCD are as follows: (i) it consists of a multitude of closely related structures, (ii) the entire complex is the active pharmaceutical ingredient, (iii) its properties cannot be fully characterized by physico-chemical analysis, and (iv) the well-controlled, robust manufacturing process is fundamental to reproduce the product.[72,73]

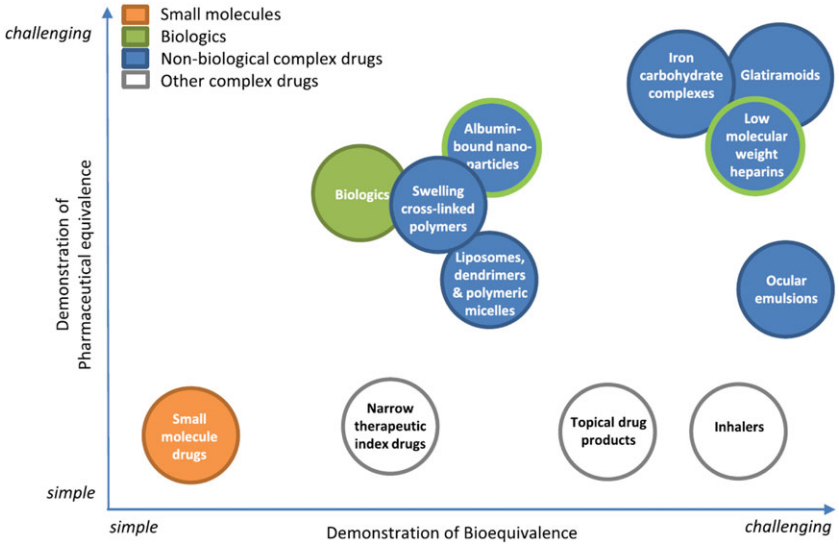
Moreover, i.v. iron complexes are prodrugs from which the active moiety, that is, iron, is liberated through a metabolic process. After entering the blood circulation, i.v. iron complexes are taken up by resident macrophages of the reticuloendothelial system (RES) in the liver, spleen, and bone marrow.[74,75] Actually, the clinical properties of i.v. iron complexes (e.g. pharmacokinetics, pharmacodynamics, and interactions with the innate immune system) are thought to be determined by a wide range of factors such as the product-specific carbohydrate as well as the size, size distribution, surface charge, and morphology of the iron nanoparticles.[76,77] Accordingly, an i.v. iron product is not only defined by its carbohydrate or the amount of incorporated iron but in large parts also by its manufacturing process that substantially influences the aforementioned properties of the iron nanoparticles.

How do differences in the physico-chemical properties of the intravenous iron complexes affect their clinical efficacy and tolerability?

The significant differences in safety and efficacy between IS originator and ISSs[41–44] support the concept that it is impossible to make exact copies of NBCDs, as their specific structures and distinct properties depend on a complex multistep manufacturing process. Furthermore, it is currently not known to which extent variations in physico-chemical properties are responsible for the observed clinical differences.

As the various originator i.v. iron complex drugs have specific compositions (*Table 1*)[20,24] and, thus, are metabolized in a complex-specific way,[21] even greater differences in the clinical efficacy and tolerability among originator products are anticipated. Considering the significantly different pharmacokinetic profiles of different iron-carbohydrate complexes (*Table 1*), these drugs are obviously not bioequivalent. For non-dextran-based i.v. iron complexes, higher molecular weight (FCM vs. SFG and IS) correlates with longer terminal half-life. Dextran/dextran-based complexes do not show such a correlation, having relatively long terminal half-lives regardless of molecular weight. These differences are likely attributable to differences in their metabolism: Upon injection, the carbohydrate part of non-dextran-based i.v. iron complexes

Figure 2 The landscape of complex drugs arranged by the challenge to assess pharmaceutical equivalence (PE) and bioequivalence (BE) between a reference product and its follow-on version.[69] For conventional low-molecular-weight drugs that can be fully characterized (orange), demonstration of PE and BE is relatively simple. For biologics (green) and the majority of non-biological complex drugs (NBCDs) (blue), both PE and BE are more difficult to demonstrate. Complex drugs are shown in blue (NBCDs) or white (other complex drugs). The classification of some NBCDs such as albumin-bound nanoparticles and low-molecular-weight heparins (blue with a green outline) varies across different countries (figure reproduced from Hussaarts *et al.*[69]).



either partly dissociates from the iron core (IS and SFG) spontaneously or is partially degraded (FCM) before core uptake by RES macrophages, whereas dextran-based complexes are taken up essentially intact by RES macrophages.[21] However, it is currently not known whether these evident differences in the pharmacokinetic profiles have an impact on the clinical efficacy and tolerability of the various originator i.v. iron complexes.

Regulatory considerations of intravenous iron products in the framework of non-biological complex drugs

Because of the specific characteristics of NBCDs, regulatory evaluation of follow-on products of this new class of drugs is challenging and cannot be based on the regulatory framework used for small molecule medicines.[69,72,78,79] Thus, it has been suggested that for the marketing authorizations of NBCD follow-on products, similar requirements as for biosimilars and a stepwise approach should be used. Accordingly, comparative animal and/or clinical studies in relevant patient populations are needed to show similarity in quality, safety, and efficacy between originator and 'similar' products.[80]

The challenges in the regulatory evaluation of follow-on i.v. iron products governing the assessment of similarity and the extent of therapeutic equivalence have been acknowledged by the regulatory agencies in Europe and the USA.[81–84] The European Medicines Agency recently published a final reflection paper highlighting its concerns regarding the current experimental and regulatory assessment of follow-on iron-based nanoparticles for the treatment of ID.[81] European Medicines Agency listed data requirements for the evaluation of therapeutic equivalence between two products, proposing quality, non-clinical and clinical bioequivalence studies to provide the necessary assurance of similarity between two products. Quality attributes to be assessed include stability of the iron–carbohydrate complex, that is, labile iron content, and various physico-chemical properties of the iron core, the compound-specific carbohydrate, and the whole iron–carbohydrate complex. The non-clinical analysis should include bio-distribution studies in a relevant animal model. The clinical studies should encompass comparison of pharmacokinetics with the reference product in a single-dose parallel or crossover study. If the results of the quality, non-clinical and clinical bioequivalence studies show minor differences between the products, a therapeutic equivalence study might be necessary to address the possible impact on efficacy and safety.

Similarly, the FDA has published draft guidance for industry, covering assessments and suggestions for bioequivalence testing of three i.v. iron products (IS, FMX, and SFG).[82–84] FDA recommends establishment of sameness in physico-chemical properties by *in vitro* characterization of the iron core, carbohydrate part, particle morphology, and labile iron content. In addition, a randomized single-dose parallel study in healthy humans assessing product-dependent iron parameters in plasma or serum is recommended. Interestingly, in 2011, FDA approved Nulecit™, the first follow-on SFG. However, in April 2013, FDA issued a 'Sources Sought' notice to evaluate the therapeutic equivalence of Nulecit™ to the SFG originator (Ferrlecit®).[85]

Interchangeability, switchability, and substitution among intravenous iron products

Interchangeability refers to the use of different medicinal products for the treatment of the same condition within the same population based on proven therapeutic equivalence. Switchability refers to the use of interchangeable products in an individual patient during the course of a treatment. This switchability is a precondition for a substitution policy.[72] With respect to i.v. iron products, pharmaceutical equivalence does not necessarily imply bioequivalence, and therefore, neither interchangeable use of nor switching between i.v. iron products is recommended.

For follow-on i.v. iron products, which are similar but not identical to the originator, the level of similarity has to be taken into consideration when deciding upon interchange and substitution. In the absence of a clear correlation between quality attributes and clinical outcome, only a sufficiently powered head-to-head clinical investigation in an appropriate patient population will provide the necessary data to assess therapeutic equivalence and proof of switchability.[71] Moreover, an underlying chronic disease may influence the iron homeostasis in general and also the metabolism of i.v. iron complexes.[21] A clinical assessment in a sensitive patient population, such as CHF, should be conducted for obtaining marketing authorization for a new iron–carbohydrate complex as well as for follow-on/similar products.[86]

However, such a sensitive approach does not always take place. In Germany, substitution at the pharmacy level between FCM and IIM is now allowed,[87] albeit these products have different active ingredients and therefore unknown differences in their metabolism as well as immunological effects in different patient populations. Notably, undesirable effects mentioned in the current product

label of IIM are based on another i.v. iron product's safety data because clinical data on IIM itself are limited.[88]

Conclusions

The key question of this review was whether study results obtained with a specific i.v. iron product for a specific condition, such as CHF, can be considered as reference for other i.v. iron products that lack comparable study data. Currently, FCM is the only i.v. iron product, which has been extensively studied in the vulnerable CHF patient population with ID/IDA in two double-blind, placebo-controlled (and one assessor-blinded standard-of-care-controlled) clinical trials and which resulted in sustainable improvement in functional capacity, symptoms, and QoL as well as in significant reduction in hospitalizations for worsening HF. FCM is also the only i.v. iron product recommended by the ESC guidelines for the treatment of CHF patients with ID. Among the different i.v. iron originator products on the market, there are large differences in their physicochemical characteristics that possibly influence their pharmacological activities. Even between originator and follow-on i.v. iron products (IS vs. ISS), differences in clinical efficacy and tolerability have been reported. Considering the lack of pivotal placebo-controlled and even more comparative head-to-head trials with other i.v. iron products in the highly vulnerable population of patients with HF, substitution of FCM with a different product is currently not recommended.

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Conflict of interest

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