Ferric carboxymaltose in iron deficient heart failure patients: a meta-analysis of individual-patient data from randomised clinical trials

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BACKGROUND

Despite optimal conventional therapy, many patients with chronic heart failure (CHF) are subject to high rates of hospitalisations and mortality which leads to substantial, epidemic public health burdens and problems.[1,2] The relevance and importance of non-cardiac co-morbidities in CHF patients has been recently developed upon.[3,4]

Iron deficiency (ID) is one of the most common co-morbidities occurring in approximately 50% of patients with CHF.[5,6] Iron plays a central role in the uptake, transport, storage and metabolism of oxygen, erythropoiesis, and cellular immune response.[7,8] At the cellular level, ID results in reduction of enzymatic activity of both the Krebs Cycle and respiratory chain in the mitochondria. As a consequence, ID leads to disturbance in the energetic metabolism of the cells.[9] In CHF patients, ID is associated with reduced exercise capacity, impaired quality of life (QoL) and poor prognosis.[5,10–13]

CONFIRM-HF and FAIR-HF, two double-blind randomised, clinical trials (RCTs) have shown improvements in functional capacity, symptoms QoL in patients with systolic CHF with ID when treated with intravenous (i.v.) ferric carboxymaltose (FCM).[14,15] However, only limited data is available on the effect on morbidity and mortality when treating ID with i.v. iron.[16]

Data from all double-blind RCTs in patients with systolic HF and ID and which were completed up to December 2014 are included in this meta-analysis on individual patient data to explore the effect of i.v. FCM relative to placebo on hospitalisations and mortality.

METHODS

Individual patient data were extracted from four completed RCTs comparing FCM with placebo in CHF patients with ID. The primary outcome was the composite of cardiovascular (CV) hospitalisations and CV death. Secondary outcomes included specific causes of hospitalisation and death. The main analysis of recurrent events are backed up by time-to-first event analyses.

Study design and inclusion criteria

Up to December 31st 2014, four double-blind RCTs investigating FCM compared to placebo in ambulatory, systolic CHF patients with ID have been conducted and completed and are included in this meta-analysis. The study design features are shown in Table 1. Before preparing and analysing the combined dataset, a detailed statistical analysis plan was prepared.

Study efficacy outcomes

The primary efficacy outcome was the composite of all cardiovascular (CV) hospitalisations and CV deaths. Secondary outcomes included the composites: HF hospitalisation and CV death, CV hospitalisation and all-cause death and, HF hospitalisation and all-cause death in addition to the individual composite components.

For each RCT, hospitalisations and cause of death were independently adjudicated in a blinded manner by an adjudication committee using the same pre-defined criteria detailed in an adjudication charter.

Safety outcomes

Safety outcomes focussed on the incidence and frequency of adverse events and on the MedDRA System Organ Classes (SOCs) Infections and Infestations, Gastrointestinal disorders and Neoplasms benign, malignant and unspecified, in addition to the occurrence of hypersensitivity reactions.

Statistical analysis

The primary efficacy analysis was conducted using the Full Analysis Set (FAS), which was defined as all randomised patients who had received at least one dose of study treatment and for whom at least one post-baseline value was available. The Safety Analysis Set (SS) was defined as all patients who were randomised and received at least one dose of study drug. For the safety analysis, treatment classification was based on treatment actually received.

Event rates were analysed using a log-link negative binomial regression model. The model included fixed covariates of treatment, Hb at baselines, region, and random effect for study. Time-to-first event analyses were also performed using Cox-models fitted with fixed effects of treatment, Hb at baseline, region and random study effect.

Adverse event incidences were presented as total number of events, patients with at least one event and the event rate per 100 patient-years.

	FAIR-HF	FER-CARS-01	EFFICACY-HF	CONFIRM-HF
Patient population	Ambulatory, optimally treated systolic CHF with ID, NYHA class II/III	Ambulatory, optimally treated systolic CHF with ID, NYHA class II/III, renal dysfunction (eGFR< 60 ml/min per 1-73m^2)	Ambulatory, optimally treated systolic CHF with ID, NYHA class II/III	Ambulatory, optimally treated systolic CHF with ID, NYHA class II/III
Randomisation	2:1 (FCM:placebo)	1:1 (FCM:placebo)	1:1 (FCM:placebo)	1:1 (FCM:placebo)
Number of patients (FAS) FCM/Placebo	304/155	30/15	20/14*	150/151
Comparator	i.v. FCM vs. placebo	i.v. FCM vs. placebo§	i.v. FCM vs. placebo	i.v. FCM vs. placebo
Study duration	24 weeks	12 weeks	24 weeks	52 weeks
Calculation of iron repletion dose	Ganzoni formula using the mean of two baseline Hb values	Ganzoni formula using the mean of two baseline Hb values	Ganzoni formula using the mean of two baseline Hb values	Determined by baseline Hb values and screening body weight
Correction phase (i.e. until iron repletion)	Over three to maximally nine weeks: weekly i.v. injections (200 mg/100 mg) of FCM/placebo	For maximally four weeks: weekly i.v. injections (200 mg/100 mg) of FCM/placebo	Over three to maximally nine weeks: weekly i.v. injections (200 mg/100 mg) of FCM/placebo	Over a six week period, maximally two i.v. injections (500 mg/1000 mg) of FCM/placebo
Maintenance phase	4-weekly 200 mg iron i.v. injection (FCM/placebo) up to 24 weeks after randomisation	4-weekly 200 mg iron i.v. injection (FCM/placebo) up to 12 weeks after randomisation	4-weekly 200 mg iron i.v. injection (FCM/placebo) up to 24 weeks after randomisation	3-monthly 500 mg iron i.v. injection (FCM/placebo) up to 36 weeks after randomisation, if ID still present
Primary endpoint(s)	PGA at Week 24 and NHYA class from baseline to Week 24	PGA at Week 24 and NHYA class from baseline to Week 24	Change in 6MWT and NHYHA class from baseline to Week 24	Change in 6MWT from baseline to Week 24

Table 1 – Design features of the RCTs included in this meta-analysis

CHF=chronic heart failure. ID= iron deficiency . NYHA=New York Heart Association. eGFR=estimated glomerular filtration rate. FCM=ferric carboxymaltose., IS=iron sucrose. FAS=Full Analysis Set. i.v.=intravenous. Hb=haemoglobin. PGA=Patient Global Assessment. 6MWT=six-minute walk test. RCT=randomised clinical trial. Ganzoni formula of total iron deficit [mg] = body weight (b.w.) [kg] x (150 - actual Hb [g/L]) x 0.24 + 500 [mg]. Iron repletion dose=correction of iron deficiency. * EFFICACY-HF was discontinued due to recruitment issues. § Placebo = i.v. normal saline.

RESULTS

Efficacy outcomes

Table 2 shows the baseline characteristics and concomitant medications of the pooled data for patients randomly allocated to FCM or placebo.

Variable	FCM (n=504)	Placebo (n=335)
Demographics		
Age (years)	68·0 (10·1)	68·3 (10·3)
Women	246 (49%)	169 (50%)
Caucasian	502 (100%)	334 (100%)
Clinical features/physical findings		
NYHA		
II	146 (29%)	128 (38%)
III	354 (70%)	205 (61%)
IV	4 (1%)	2 (1%)
LVEF (%)	33·3 (6·9)	34·5 (7·1)
Body-mass index (kg/m^2)	27·9 (4·7)	28·3 (5·4)
6-minute walk distance (m)	277 (105)	284 (106)
Cardiovascular risk factors		
Hypertension	411 (82%)	283 (84%)
Dyslipidaemia	258 (51%)	182 (54%)
Diabetes mellitus	148 (29%)	93 (28%)
Smoking	145 (29%)	92 (27%)
Medical history		
Atrial fibrillation	179 (36%)	126 (38%)
Myocardial infarction	270 (54%)	183 (55%)
Angina pectoris	300 (60%)	194 (58%)
Stroke	46 (9%)	37 (11%)
Coronary revascularisation	116 (23%)	73 (22%)
Laboratory test results		
Hb (g/dL)	12·08 (1·34)	12·20 (1·34)
Hb <12 g/dL	228 (45%)	142 (42%)
Ferritin (ng/mL)	54·8 (52·3)	59·9 (56·6)
Ferritin <100 ng/mL	448 (89%)	292 (87%)
TSAT (%)	18·5 (14·1)	17·5 (8·5)
TSAT ≤ 20%	338 (67%)	220 (66%)
eGFR (CKD-EPI) (mL/min per 1·73m^2)	62·9 (21·3)	63·1 (22·6)
eGFR < 60 mL/min per 1.73m^2	216 (43%)	156 (47%)
Concomitant treatment		
Diuretics	465 (92%)	307 (92%)
Angiotensin-converting-enzyme inhibitor or angiotensin-receptor blocker	473 (93%)	313 (93%)
Beta-blocker	438 (86%)	294 (88%)
Aldosterone antagonists	278 (55%)	174 (52%)
Digitalis glycoside	94 (19%)	80 (24%)
Antithrombotic agents	433 (85%)	290 (87%)
Lipid-lowering therapy	272 (54%)	272 (54%)
Diabetic therapy	125 (25%)	83 (25%)

Table 2 – Baseline characteristics

Data are number of patients (%) or mean (SD) unless otherwise indicated. FCM=ferric carboxymaltose. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction functional class. Hb=haemoglobin. TSAT=transferrin saturation. eGFR=estimated glomerular filtration rate.

Table 3 shows the results for total hospitalisations (including repeats) and mortality. Compared to placebo, FCM significantly reduced the rate of the following: CV hospitalisations and CV death, of HF hospitalisations and CV death, or CV hospitalisations and all-cause death, and of HF hospitalisations and all-cause death.

Recurrent event outcomes	FCM* (n=504)	Placebo* (n=335)	Rate ratio (95% CI)	p
CV hospitalisation and CV death	69 (23·0)	92 (40·9)	0·59 (0·40–0·88)	0·009
HF hospitalisation and CV death	39 (13·0)	60 (26·7)	0·53 (0·33–0·86)	0·011
CV hospitalisation and all-cause death	71 (23·7)	94 (41·8)	0·60 (0·41–0·88	0·009
HF hospitalisation and all-cause death	41 (13·7)	62 (27·6)	0·54 (0·34–0·87)	0·011
All-cause hospitalisation and all-cause death	108 (36·1)	118 (52·5)	0·73 (0·52–1·01)	0·060
HF hospitalisation	22 (7·3)	43 (19·1)	0·41 (0·23–0·73)	0·003
CV hospitalisation	52 (17·4)	75 (33·3)	0·54 (0·36–0·83)	0·004
All-cause hospitalisation	89 (29·7)	99 (44·0)	0·71 (0·50–1·01)	0·056

Table 3 – Rate ratio analysis for primary and secondary outcomes (recurrent event analyses)

FCM=ferric carboxymaltose. CI=confidence interval. CV=cardiovascular. HF=heart failure.
* Total number of events (incidence per 100 patient-years of follow-up)

Table 4 shows the data for the time-to-first event analysis. Compared to placebo, the occurrence of HF hospitalisations or CV death were less frequent in patients assigned to FCM as were HF hospitalisations or all-cause death.

Outcomes	FCM* (n=504)	Placebo* (n=335)	Hazard ratio (95% CI)	p
CV hospitalisation or CV death	55 (18·4)	59 (26·2)	0·70 (0·48–1·02)	0·062
HF hospitalisation or CV death	32 (10·7)	44 (19·6)	0·55 (0·35–0·88)	0·012
CV hospitalisation or all-cause death	57 (19·0)	61 (27·1)	0·70 (0·49–1·02)	0·060
HF hospitalisation or all-cause death	34 (11·4)	46 (20·4)	0·56 (0·36–0·88)	0·013
All-cause hospitalisation or all-cause death	81 (27·0)	75 (33·3)	0·81 (0·59–1·12)	0·199
HF hospitalisation	19 (6·3)	34 (15·1)	0·42 (0·24–0·74)	0·003
CV hospitalisation	43 (14·4)	52 (23·1)	0·61 (0·40–0·91)	0·017
All-cause hospitalisation	68 (22·7)	67 (29·8)	0·75 (0·53–1·06)	0·099
CV death	17 (5·7)	17 (7·6)	0·84 (0·43–1·66)	0·620
All-cause death	19 (6·3)	19 (8·4)	0·84 (0·44–1·61)	0·604

Table 4 – Time-to-first event outcomes

FCM=ferric carboxymaltose. CI=confidence interval. CV=cardiovascular. HF=heart failure.
* Total number of events (incidence per 100 patient-years of follow-up)

Safety outcomes

Table 5 shows that the proportion who experienced at least one adverse event (AE) – with an incidence rate per 100 patient-years at risk for FCM and placebo that was similar.

Safety reporting	FCM (n=507)		Placebo (n=335)	
	# Patients with event (%)	Incidence per 100 patient-years at risk	# Patients with event (%)	Incidence per 100 patient-years at risk
Adverse events	317 (62·5%)	105·4	215 (64·2)	95·8
Serious adverse events	86 (17·0)	28·6	79 (23·6)	35·2
Adverse events leading to study drug withdrawal	32 (6·3)	10·6	34 (10·1)	15·1
Study-drug related AEs	50 (9·9)	16·6	20 (6·0)	8·9
Serious drug-related AEs	0	0	1 (0·3)	0·4
Study drug-related leading to study drug withdrawal	7 (1·4)	2·3	3 (0·9)	1·3

Table 5 – Investigator-reported adverse events

FCM=ferric carboxymaltose. #=number.

The proportion of patients who experienced at least one event in the MedDRA SOC "Infections/Infestations", "Gastrointestinal disorders" and "Neoplasms benign, malignant and unspecified" was similar between the two treatment groups, 18·7% vs. 23·0%, 9.1% vs. 6.9% and 1.2% vs 1.8% for the FCM and placebo groups respectively. No serious or severe hypersensitivity reactions were reported for any patient from either treatment group.

Based on the baseline ID values, the mean FCM dose needed to correct the ID was 1,327 (329) mg. The overall mean (SD) cumulative FCM dose administered was 1,679 (522) mg.

CONCLUSION

Treatment with FCM compared to placebo reduces the rate of CV hospitalisations and CV mortality in ambulatory patients with systolic CHF with ID. A well-designed and adequately powered RCT is needed to confirm these findings.

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