A Multicenter Prospective Double Blinded Randomized Controlled Pilot Trial of Intravenous Iron (Ferric Derisomaltose (FDI)) in Iron Deficient but not Anemic Patients with Chronic Kidney Disease on Functional Status.

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Abstract

Background

Iron deficiency (ID) is common in patients with chronic kidney disease (CKD). Intravenous (IV) iron in heart failure leads to improvement in exercise capacity and improvement in quality of life measurements; however, data in patients with CKD are lacking.

Methods

The Iron and the Heart Study was a prospective double blinded randomized study in non-anemic CKD stages 3b-5 patients with ID which investigated whether 1000 mg of IV iron (ferric derisomaltose (FDI)) could improve exercise capacity in comparison to placebo measured at 1 and 3 months post infusion. Secondary objectives included effects on hematinic profiles and hemoglobin, safety analysis and quality of life questionnaires (QoL).

Results

We randomly assigned 54 patients mean (SD) age for FDI (n=26) 61.6 (10.1) years vs placebo (n=28; 57.8 (12.9) years) and mean eGFR (32.1 (9.6) vs. 29.1 (9.6) ml/min/1.73m^2) at baseline, respectively. Adjusting for baseline measurements, six-minute walk test (6MWT) showed no statistically significant difference between arms at 1 month (p=0.736), or 3 months (p=0.741). There were non-significant increases in 6MWT from baseline to 1 and 3 months in the FDI arm. Hemoglobin (Hb) at 1 and 3 months remained stable. There were statistically significant increases in ferritin (SF) and transferrin saturation (TSAT) at 1 and 3 months (p<0.001). There was a modest numerical improvement in QoL parameters. There were no adverse events attributable to IV iron.

Conclusion

This study demonstrated a short-term beneficial effect of FDI on exercise capacity, but it was not significant despite improvements in parameters of iron status, maintenance of Hb concentration, and numerical increases in functional capacity and quality of life scores. A larger study will be required to confirm if intravenous iron is beneficial in iron deficient non-anemic non-dialysis CKD patients without heart failure to improve the 6MWT.

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Significance Statement

It is not known if administration of 1000 mg of intravenous iron versus placebo solution improves the six-minute walk test (6MWT) in patients with established chronic kidney disease (CKD) stages 3b-5, who are iron deficient but not anemic.

This prospective double blinded randomized, multi-center study in 54 patients who were given either a single dose of 1000 mg of intravenous iron or placebo solution showed that intravenous iron led to:

- a significant increased serum ferritin and transferrin saturation
- maintenance of the hemoglobin concentration
- an increased 6MWT from baseline to 1 and 3 months post infusion, but these changes were not statistically significant compared with placebo
- a modest improvement in quality of life scores
- no adverse events attributable to intravenous iron.

This study shows that intravenous iron repletes iron but is insufficient to significantly improve the 6MWT. A larger study would be advisable in this patient group.

Background

Patients with non-dialysis dependent chronic kidney disease (CKD) G3b or worse have a significant excess mortality, particularly from cardiac related causes, because of a spectrum of macrovascular structural changes, metabolic abnormalities in calcium and phosphate, hypertension, iron deficiency, anemia and volume overload (1, 2), and a high proportion have or develop heart failure. In patients with heart failure and CKD, the prevalence of anaemia is as high as 32% (3) and survival was worse in patients with iron deficiency (3) suggesting iron may be an important substrate for optimal cardiac function and reduction in cardiac risk. Several other studies in heart failure patients (4–6) have also shown that IV iron may have beneficial effects on the heart which may impact on reduced cardiovascular events, improved functional capacity and improved symptom burden. Iron is important in a number of biological processes (7–11). The potential underlying beneficial mechanism, which may in part relate to changes in skeletal energetics (12), at least in heart failure patients, has not been examined in a specific renal population. In addition, increased iron repletion appears to decrease the risk of mortality and cardiac events as seen in the PIVOTAL study in patients receiving hemodialysis (13, 14), and higher doses also seem more efficacious in patients with non-dialysis dependent CKD (15, 16).

We hypothesized that treatment with a single dose of 1000 mg of intravenous (IV) (ferric derisomaltose/iron isomaltoside 1000 (FDI); Monofer®) would benefit non-anemic patients with CKD and iron deficiency in comparison to placebo over 1 and 3 months post infusion in terms of functional capacity.

Methods

Trial Design and Oversight

We conducted this prospective, randomized, double blinded, controlled trial at 3 sites in the United Kingdom (17). The trial protocol was approved by the relevant health authorities and institutional review boards, and all the patients provided written informed consent. The trial sponsor (Hull University Teaching Hospitals NHS Trust) performed regular safety surveillance. Data were analyzed by the Department of Statistics, at the University of York, UK.

This was an academic investigator–led trial which was funded by Kidney Research UK and supported by an unrestricted grant from Pharmacosmos A/S (which also provided ferric derisomaltose/iron isomaltoside for the trial).

This study was carried out in accordance with Good Clinical Practice guidelines, the Declaration of Helsinki, and received ethical approval from the Northern Regional Ethics Service (NRES) Committee Yorkshire & The Humber - Leeds East, UK), approval reference number REC no: 14/YH/1209.

Study Participants

Adults with established non dialysis dependent CKD stages G3b-5 who had a serum ferritin (SF) of less than 100mcg/L and/or a transferrin saturation (TSAT) of less than 20% but no anemia (defined in this study as a hemoglobin (Hb) 110–150 g/L for both males and females) were eligible to participate. The full eligibility criteria are provided in the protocol (17).

A second group consisting of a “control” group of patients with CKD and no anemia or iron deficiency allowed for baseline comparisons, while a third group of healthy patients served as baseline controls (healthy volunteers with no known underlying disease or chronic kidney disease as judged by their suitability for transplant donation during live transplant donor work up).

Randomization, Treatment, and Follow-up

The randomization was performed by a computer program (sealedenvelope.com). We randomly assigned participants, in a 1:1 ratio, to receive a 100 ml infusion of either 1000 mg of IV iron (FDI) or 100 ml of placebo solution in a blinded fashion as described in the methods paper (17); patients were evaluated at baseline, 1 and 3 months. Managing clinicians treated patients’ CKD according to standard practice.

Study Procedures

These are detailed in the methods paper (17) but in brief Group 1 and Group 2 patients underwent assessments at baseline, 1 month and 3 months while Group 3 underwent baseline tests only. These consisted of the 6-minute walk test (6MWT), laboratory measurements including eGFR and biochemical profile (BCP), full blood count (FBC), hemoglobin (Hb), serum ferritin (SF), transferrin saturation (TSAT), C-reactive protein (CRP) and NT-ProBNP and cystatin C. Quantification of proteinuria was carried out by measurement of urinary protein:creatinine ratio (uPCR) or if diabetic, urinary albumin:creatinine ratio (uACR). New York Assocaition Functional classification (NYHA), electrocardiogram (ECG) and 2D echo were carried out in all Group 1 patients at baseline, 1 and 3 months. Three questionnaires: the Kidney Disease Quality of Life Short Form Questionnaire (KDQoL-SF-36), The Minnesota Living with Heart Failure Questionnaire (MLHF), and the Restless leg syndrome scale questionnaire (RLSS) were completed at the three time points for Groups 1 and 2 and at baseline only for Group 3. Pulse wave velocity (PWV) and augmentation index (AiX) measurements were performed at baseline and at months 1 and 3 for Groups 1 and 2.

Trial Endpoints

The primary endpoint was based on functional capacity at 1 and 3 months, assessed by the 6MWT, in patients receiving a single dose of 1000 mg of IV FDI or infusion of placebo. This required 48 participants (24 per group) to detect a 25 meter (m) increase in 6MWT between the intervention and control group with 80% power at a 5%, 2-sided significance level.

Secondary endpoints consisted of efficacy endpoints which included changes in SF, TSAT and Hb concentrations, and 3 questionnaires: KD-QOL SF-36, RLSS, and MLHF.

Safety endpoints included death, infections, vascular access thrombosis, hospitalization for any cause, and hospitalization for infection, each assessed during the whole study period. Data on serious adverse events were collected prospectively, and events were coded with the use of the *Medical Dictionary for Regulatory Activities* (MedDRA), version 15.1. Data on non-serious adverse events, other than infection and vascular access thrombosis, were not collected.

Statistical Analysis

All data was analysed in accordance with an intention-to-treat principle wherein data from any randomized participant was included in the arm to which they were randomized. Continuous laboratory parameters were summarized using mean (standard deviations), or median with interquartile ranges (25th and 75th percentile). Categorical variables were summarized using number (%). For the primary outcome measure, 6MWT, ANCOVA was used to compare groups at 1 month and 3 months, adjusting for baseline 6MWT. The absolute change from baseline to the 1 month and 3 months was compared using a t-test. Repeated measure ANOVA was used to compare the change across baseline, 1 month and 3 months. ANCOVA was also used for the secondary outcomes. A p-value of < 0.05 was considered to

indicate statistical significance. All analyses were undertaken using IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, N.Y., USA).

Results

Patients: Baseline characteristics

The patient disposition consort figure was published previously (17) but in brief, of the 316 patients who were screened for entry into the trial, 261 did not meet the criteria for randomization, declined to participate or were not eligible. One patient consented but did not enter the study. A total of 54 patients were randomly assigned to the main study group 1 (26 patients to FDI and 28 patients to the placebo) and constituted the intention-to-treat population. Follow-up was complete for all patients except 2 who missed their final follow-up visit, but all patients did not carry out all tests.

The characteristics of the 2 arms of Group 1 (the study group) were similar at baseline, although there was a 4 years age difference with the FDI group (n = 26; mean (SD) age 61.6 (10.1) years) vs the placebo group (n = 28; mean (SD) age 57.8 (12.9) years). Mean (SD) serum creatinine was 167.0 (40.2) vs. 204.9 (67.3) micromol/L and eGFR 33.2 (9.6) vs. 29.1 (9.6) ml/min/1.73 m^2 at baseline in FDI and placebo treated patients, respectively. There was a difference in the mean (SD) baseline distance covered during the 6MWT (386.6 (135.8) meters in FDI vs 414.7 (104.5) meters in placebo treated patients; Table 1).

Table 1

Baseline Demographic Data; Mean (Standard deviation) n, or number (%) for the total for group 1 and unblinded data; the 2 control groups (2 and 3). uACR/uPCR = urinary albumin/protein:creatinine ratio. eGFR = Estimated glomerular filtration rate; CRP = C-Reactive Protein. 6MWT = Six-minute walk test. MLHF = Minnesota Living and Heart Failure Questionnaire. RLSS = Restless leg syndrome scale. ECG: N = Within normal limits; NCS = Abnormal and not clinically significant; ACS = Abnormal and clinically significant. FDI = Ferric Derisomaltose

Group and number of participants	**FDI or Placebo** **N = 54** **CKD, no anemia but iron deficiency**	**FDI** **N = 26**	**Placebo** **N = 28**	**Control** **Group 2** **N = 10** **CKD no anemia & no Iron deficiency**	**Control** **Group 3** **N = 10**
Age (years)	59.6 (11.7) n = 53	61.6 (10.1) 37–78	57.8 (12.9) 32–78	60.0 (11.1)	50.7 (11.8)
Sex					
Male	26 (49%)	11 (42.3%)	15 (53.6%)	5 (50%)	5 (50%)
Female	27 (51%)	14 (53.8%)	13 (46.4%)	5 (50%)	5 (50%)
Unknown	1	1	0	0	0
Ethnicity					
White	42 (78%)	19 (73.1%)	23 (82.1%)	9 (90%)	10 (100%)
Asian	3 (5%)	1 (3.8%)	2 (7.1%)	0	0
Black	7 (13%)	4 (15.4%)	3 (10.7%)	1 (10%)	0
Mixed Race	1 (2%)	1 (3.8%)	0 (0%)	0	0
Unknown/other	1 (2%)	1 (3.8%)	0 (0%)	0	0
Smoker					
Yes current	5 (9%)	1 (3.8%)	4 (14.3%)	2 (20%)	0 (0%)
Yes previous	17 (32%)	8 (30.8%)	9 (32.1%)	3 (30%)	4 (40%)
No	32 (59%)	17 (65.4%)	15 (53.6%)	5 (50%)	6 (60%)

Group and number of participants	FDI or Placebo N = 54 CKD, no anemia but iron deficiency	FDI N = 26	Placebo N = 28	Control Group 2 N = 10 CKD no anemia & no Iron deficiency	Control Group 3 N = 10
Body Mass Index (BMI)	30.3 (6.5), 53	30.7 (6.8)	30.01 (6.4)	29.4 (5.4)	26.8 (2.94)
Serum Ferritin (SF) (microg/L)	66.3 (44.1) 53	64.2 (29.1) 26	68.4 (55.3) 27	221.2 (110.9)	76.1 (63.8)
Transferrin Saturation % (TSAT)	20.1 (7.4) 53	22.3 (8.8) 26	19.7 (5.6) 27	27.4 (8.5)	27 (11.3)
Hemoglobin (Hb) (g/L)	128.7 (10.1), 54	131 (7.4), 26	126.6 (11.8), 28	121.5 (12.3)	138.2 (14.08)
Serum Creatinine (micromol/L)	186.7 (58.6), 54	167 (40.2), 26	204.9 (67.3), 28	189 (50.01)	72.8 (14.9)
eGFR (ml/min/1.73 m^2)	31.1 (9.6), 54	33.2 (9.3), 26	29.1 (9.6), 28	31.5 (9.2)	87.5 (6.1)
Cystatin C	2.2 (0.6), 52	2.1 (0.5), 26	2.4 (0.6), 26	2.52 (0.33)	0.95 (0.11)
uACR (mg/mmol)	60.9 (133.3), 26	26.9 (40), 13	94.8 (181.4), 13	26.6 (37.3)	1.26 (1.93)
uPCR (mg/mmol)	83.8 (128.4), 40	51.9 (59.3), 19	112.7 (164.8), 21	51.7 (39.0)	11.4 (5.8)
CRP (mg/L)	5.0 (4.4), 53	6.3 (5.5), 26	3.8 (2.4), 27	4.9 (5.2)	3.65 (4.8)

Group and number of participants	FDI or Placebo N = 54 CKD, no anemia but iron deficiency	FDI N = 26	Placebo N = 28	Control Group 2 N = 10 CKD no anemia & no Iron deficiency	Control Group 3 N = 10
Serum Albumin (g/L)	39.8 (5.6)	40.8 (4.2)	38.8 (6.9)	37.8 (1.55)	39.5 (2.68)
Platelet count **($X10^5$)**	235 (58.9)	226 (52.4)	243 (64.1)	244.3 (79.9)	261.4 (60.75)
Phosphate **(mmol/L)**	1.2 (0.2)	1.1 (0.2)	1.2 (0.2)	1.05 (0.24)	1.12 (0.11)
NT pro BNP **(ng/L)**	485.2 (1268.4), 51	422.5 (881.9), 25	545.4 (1569.5), 26	1041.0 (993.6)	98.0 (99.4)
PWV measurement	8.3 (3.2), 54	8.3 (2.8), 26	8.3 (3.6), 28	7.24 (2.62)	6.6 (1.53)
AiX measurement	24.2 (10.7) 54	25.4 (10.7) 26	24.1 (10.8) 28	23.7 (16.1)	17 (10.78)
6MWT Metres (m)	401.2 (120.2), 52	386.6 (135.8), 25	414.7 (104.5), 27	392.6 (158.5)	528.4 (87.3)
KD-KQoL SF36 **(normalised data)**	40.2 (10.4), 48	40.2 (10.4), 21	40.4 (9.55), 27	46.9 (8.7), 10	56.3 (6.2), 10
MLHF	23.97 (26.3)	22.7 (25.7) 18	25.0 (27.3) 24	29.6 (23.7)	1.88 (5.3)
RLSS	9.670 (10.3)	9.5 (10.4) 20	9.8 (10.4) 23	6.8 (12.4)	1.8 (5.69)

Group and number of participants	FDI or Placebo N = 54 CKD, no anemia but iron deficiency	FDI N = 26	Placebo N = 28	Control Group 2 N = 10 CKD no anemia & no Iron deficiency	Control Group 3 N = 10
Systolic Blood Pressure (mmHG)	133.6 (19.5), 54	138.2 (19.9), 26	129.4 (18.4), 28	143.8 (13.6)	126.8 (17.2)
Diastolic Blood Pressure (mmHG)	77.3 (11.3), 54	78.5 (10.7), 26	76.2 (11.8), 28	81.1 (6.4), 26	79.6 (13.9), 28
Baseline ECG					
N	38	17	21	4	10
NCS	13	8	5	6	0
ACL	1	1	0	0	0
Not Recorded	2	0	2	0	0
Etiology of renal disease in whole cohort of patients in all groups					
Diabetes	17	8	9	2	0
Hypertension	4	2	2	1	0
Polycystic Kidney Disease	5	2	3	2	0
Pyelonephritis/Reflux	3	1	2	1	0
Glomerulonephritis / IgA/vasculitis/interstitial nephritis	14	8	6	2	0
Other/unknown	11	5	6	1	0

In the additional control groups, the mean (SD) age of Group 2 (patients with CKD, no iron deficiency and no anemia) was similar to Group 1 at 60 (11.1) years, but this was a decade older than Group 3 (healthy controls) in whom the mean (SD) age was 50.7 (11.8) years. The CKD patients in Group 2 walked approximately 130 meters less on average during the 6MWT (mean (SD) 392.6 (158.5) meters compared to the healthy control subjects (528.4 (87.3) meters); (Table 1).

Primary endpoint: 6MWT

Adjusting for baseline 6MWT, the 6MWT in the main study participants (Group 1) at 1 month and 3 months showed no statistically significant difference between FDI and placebo arms (p = 0.736 and 0.741 respectively). Using a repeated measure ANOVA, with baseline, 1-month and 3-month data (18 FDI patients and 24 placebo patients), there was no significant difference between the arms of Group 1 (p = 0.124). (Fig. 1). Analysis of change in 6MWT showed that the mean (SD) change for FDI patients from baseline to 3 months was 6.0 (89.1) meters compared to 1.9 (111.2) meters for the placebo arm patients; this was not significantly different **(Suppl Table 1).** During follow up there was a greater than 25 meter increase in 6MWT observed in 8/22 (36.4%) of patients at 1 month and 10/20 (50%) at 3 months in the FDI group vs 8/25 (32% – 1 month) and 10/24 (41.7% – 3 months) patients in the placebo arm, respectively (p = 0.753, p = 0.580).

Secondary efficacy outcomes

There was no statistically significant difference in Hb at 1 month (p = 0.195) and 3 months (p = 0.152) (Fig. 2 **and** Table 2). There was an upwards trend in Hb with an absolute mean increase of 1.7 g/L and 3.7 g/L with FDI compared to a fall of 1.0 g/L and 0.3 g/L in the placebo arm, thus, there was a difference of 2.7 g/L and 4.0 g/L in Hb in favor of FDI at 1 and 3 months, respectively.

Table 2
Summary of mean (SD) for hemoglobin (Hb) and hematinics; serum ferritin and transferrin saturation (TSAT) at baseline, 1 and 3 months.

		FDI			Placebo			
		Mean	SD	n	Mean	SD	n	P value
Hb	Baseline	131.0	7.4	26	126.5	11.8	28	
	1 month	132.7	7.2	24	125.5	12.8	26	0.195
	3 months	134.7	8.9	20	126.2	12.4	25	0.152
Ferritin	Baseline	64.2	29.1	26	68.4	55.3	27	
	1 month	266.0	105.8	23	70.5	55.8	26	< 0.001
	3 months	234.4	105.3	21	69.4	59.8	24	< 0.001
TSAT	Baseline	22.3	8.8	26	19.7	5.6	27	
	1 month	29.6	9.5	22	19.1	7.1	26	< 0.001
	3 months	26.4	10.5	21	18.0	6.8	23	< 0.001

There was a statistically significant difference for SF and TSAT at both 1-month ($p < 0.001$, $p < 0.001$) and 3 ($p < 0.001$ and $p = 0.001$) months, respectively, with greater increases in the FDI group (Figs. 3 and 4, Table 2).

Overall, 96% and 95% of participants achieved a SF > 100microgram/L at 1 and 3 months in the FDI group in comparison to 19% and 21% in the placebo group, respectively ($p < 0.001$, $p < 0.001$). 77% and 67% of participants achieved a TSAT > 20% at 1 and 3 months in the FDI group in comparison to 23% and 30% in the placebo group, respectively ($p < 0.001$, $p = 0.016$).

Questionnaires

The RLSS showed that patients with CKD and iron deficiency had a 5-fold higher score in comparison to healthy controls (Table 1). Those receiving IV iron had similar baseline scores to placebo in Group 1 (Table 1), and FDI led to a non-statistically significant improvement of the RLSS score compared to placebo.

The MLHF questionnaire showed that patients with CKD and iron deficiency had a 12-fold higher score in comparison to healthy controls and were therefore more symptomatic (Table 1). Those receiving IV iron had similar baseline scores to placebo in Group 1, and IV iron did not impact this score significantly **(**Table 1 **and Suppl Table 2).**

The numerical improvements at 1 and 3 months in the normalized KD-QoL-SF-36 questionnaires in FDI patients were modest but not statistically significant. At baseline, the overall component summary Measure (Physical and Mental Health) KD-QoL-SF36 scores in Group 1 were on average 15% lower than those in Group 2, and 29% lower than healthy controls in Group 3 (Table 1), thus indicating an impact of both iron deficiency and CKD, independently, on quality of life scores. At 1-month, despite the numerical increases in normalized scores (difference of 1.5), there was no significant difference between the intervention arms in Group 1 ($p = 0.981$) **(**Fig. 5 **and Suppl Table 3a).** At three months, there was a larger difference (2.3) which was not significant between the two arms of Group 1 ($p = 0.451$) **(**Fig. 5 **and Suppl Table 3a)**. Repeated measures analysis across the three time points included 14 FDI and 23 placebo patients with complete baseline, 1-month and 3-month data and there was no statistically significant difference between the two arms ($p = 0.515$) (**Suppl Table 3b)**.

Safety Analysis

Renal Function

Renal Function as assessed by serum creatinine, eGFR and cystatin C were similar in both arms of Group 1 with no statistically significant difference between FDI and placebo at 1 or 3 months. Proteinuria did not change with time or with IV iron treatment **(Suppl Table 4).**

Phosphate, albumin, platelets and CRP

Serum phosphate levels and platelet count remained stable with no significant changes throughout the study period in both FDI and placebo arms of Group 1. Serum albumin was similar in both arms of Group1 and did not change throughout the study. Mean (SD) CRP was unchanged throughout the study period; it was 4.2 (2.7) vs 6.9 (18.3) mg/L at 1-month (p = 0.6), and 7.5 (6.8) vs 10.3 (23.0) mg/L at 3 months (p = 0.46) in the FDI and placebo patients, respectively.

Blood pressure and endothelial function

Blood pressure remained stable over follow-up and was similar in both arms of Group 1 **(Suppl Table 5)**. Endothelial function measured clinically using PWV and AiX did not change at 1 or 3 months post FDI infusion or in the placebo arm **(Suppl Table 5)**.

Adverse events

A total of 19 adverse events were documented in 13 participants during the duration of the study (Table 3). This equated to 19 events in 162 patient months in the whole cohort of Group 1. There were no treatment-related serious adverse events adjudicated by the primary investigators at each site, and no deaths, strokes or hospitalizations during the study period. There were also no hypersensitivity reactions or infusion reactions with FDI.

Table 3
Summary of adverse events

Adverse Events	Total	FDI	Placebo
Infections	5 Infections consisting of one urinary tract infection (UTI); 1 lower respiratory tract infection (LRTI), 1 flu and one exacerbation of chronic obstructive pulmonary disease (eCOPD) and one shingles flare	1 flu 1 UTI, 1 infective 1 eCOPD	1 LRTI 1 shingles
Cardiovascular events	Angina x 2	0	2
Shortness of breath	2	0	2
Other	Hypoglycaemia	0	1
	Had intravenous fluid for elective CTscan	0	0
	? lung Cancer	0	1
	Gout	1	0
	Depression	1	0
	Per Rectal bleeding	0	1
	Acute Kidney Injury episode	0	1
	Cough	1	0
	Poor Blood Pressure control	1	0
		2	0
	19 in 13 patients	9 in 6 patients	10 in 7 patients

Cardiac Assessments

Patients were classified into NYHA categories I to IV, and the average was similar in both placebo and FDI arms of group1. In total 3/18 (16%) and 3/22 (14%) patients had an improvement in NYHA category in the FDI arm compared to the placebo arm, respectively after 3 months. There was only one ECG which was deemed clinically significantly abnormal at baseline during the study, and this remained unchanged throughout the study in the placebo arm. No patient manifested a change in the status of the ECG. The

standard 2-D echocardiogram results were also similar over time in the 2 randomized arms of Group 1. One echocardiogram was reported as abnormal and clinically significant at baseline in one patient and a further one in a second patient during the 3-month study period in the placebo arm of the study.

NT-Pro BNP levels were approximately 5-fold higher in patients with CKD and iron deficiency compared to healthy controls, but there was also a 2-fold difference between Group 1 and 2 and the level of NT-Pro BNP was higher in CKD patients without iron deficiency (Group 2) but this was not significant. **(**Table 1**)**. The mean (SD) NT-Pro BNP levels appeared to fall post FDI infusion (422.5 (881.9) pg/ml at baseline to 242.5 (209.1) pg/ml at 1 month) in comparison to placebo (545.4 (1569.5) pg/ml at baseline to 608.8 (1891)pg/ml at 1 month), but this did not reach significance (p = 0.371) **(Suppl Table 6).**

Discussion

The Iron and the Heart Study investigated whether a single dose of 1000 mg of IV iron (ferric derisomaltose/iron isomaltoside 1000 (FDI); Monofer®) could improve exercise capacity in comparison to placebo over 1 and 3 months in non-anemic CKD patients who had iron deficiency. Our results demonstrate several important findings in addition to the relationship between IV iron and functional capacity using the 6MWT, including quality of life.

The optimal management of iron deficiency in patients with non-dialysis dependent CKD is unclear with some evidence suggesting benefit of treatment (18). In addition, evidence of functional improvement in non-anemic iron deficient patients with CKD is lacking, as are head-to-head randomized controlled studies comparing IV iron versus placebo. In contrast to results from studies in heart failure patients (4–6), results of this trial showed no significant impact of IV FDI on 6MWT at 1 or 3 months post infusion, and only a modest but non-significant improvement in summary component score in QOL SF36 scores when compared with placebo. Hemoglobin remained stable and there were significant increases in SF and TSAT without significant changes in endothelial dysfunction, assessed by PWV.

The Kidney disease improving global outcomes (KDIGO) clinical practice guidelines recommends the use of iron therapy in CKD patients with a SF of < 500micrograms/L or a TSAT ≤ 30% if it is desired to increase Hb or to reduce erythropoiesis stimulating agent therapy (18).The National Institute of Clinical Health and Care Excellence (NICE) and the UK Renal Association have similar recommendations (19, 20). A recent higher threshold of SF of 800micrograms/L, only for hemodialysis patients, based on data from the PIVOTAL trial has been included in the revised Renal Association guidelines, but this does not apply to this study for which we cannot make any recommendations except the need for a further study with sufficient power to see if higher thresholds might have an impact on functional status in non-dialysis CKD. Our results in this population indicate that patients with CKD and iron deficiency but no anemia have worse quality of life and restless leg syndrome scores compared to healthy controls and also CKD patients without iron deficiency, and worse 6MWT scores, but the addition of 1000 mg of iron did not lead to significant benefit.

These findings may be due to several factors including the sample size, dropouts and incomplete data collection, the relatively well-preserved cardiac function, and the relatively short follow-up period. In addition, the relatively well preserved 6MWT at baseline in retrospect might have indicated the margin for improvement may have been small in comparison to heart failure trials where the baseline values were more than 100 meters less. Imputation using last observation carried forward was not significant. The dose of iron administered for iron repletion may have been insufficient to improve cellular energetics. Furthermore, there was an imbalance in baseline characteristics (age was greater and baseline 6MWT was lower in FDI patients compared with patients in the placebo group) and so we are cautious to infer any definitive conclusions.

Earlier work in heart failure patients has shown skeletal muscle improvements with IV iron (12), which may possibly not occur in uremic CKD patients as a result of the presence of various uremic toxins. The balance of effects of oxidative stress generated in chronic disease and with IV iron may have an impact although we did not see any additional impact of IV iron on clinical measures of endothelial dysfunction. Animal models suggest that in experimental CKD, in which iron deficiency may also be present, the impact of increased pro-oxidative factors is negated by antioxidant factors (21, 22). Although the heart failure trials testing iv iron dosing included patients with renal impairment, the average eGFR in our population was 30 ml/min/1.73 m^2 and thus consistent with more advanced CKD. In animal models of experimental uremia we have observed that there are marked changes in energetics, insulin resistance and mitochondrial function because of uremia (10, 11, 23–25). These may not have been reversible with a single dose of 1000 mg IV iron in the current study. The levels of NT Pro BNP fell post IV iron infusion in comparison to placebo, but the difference between the two groups did not reach statistical significance. Nevertheless, this may be an interesting signal as in a previous study of 40 patients with heart failure and modest renal impairment there was a significant reduction in NT Pro BNP with IV iron treatment (26). These findings are in line with the trends observed in the current study.

Patients assigned to treatment with FDI were no more likely to experience an adverse event than those receiving placebo treatment. This trial was not designed to determine the mechanism of any therapeutic effect of IV iron but to determine whether there was a clinical functional benefit associated with its administration. However, this trial provides valuable information for the design of a future randomized controlled trial of sufficient power to answer the question definitively.

The strengths of our trial include its double-blind nature which reduced bias, and the multiple explorative analyses carried out to direct future research. Based on the data it demonstrates that a larger scale trial would be required to reliably confirm or refute a benefit of IV iron. Limitations of the trial include the modest size of the study and short follow-up. Thus, the generalizability of the trial findings is limited, and a larger study is needed. In addition, because quality-of-life data were missing for some patients, the interpretation of the effect of the iron dose with regard to these endpoints is limited. The trial was not designed or powered to detect effects on hard clinical endpoints, but the safety demonstrated in this study would add support to the conduct of an appropriately powered event-driven study examining the effects of IV iron on patient-related outcome measures.

Conclusions

In summary, this randomized controlled trial showed that, among non-anemic patients with CKD and iron deficiency, a single dose of 1000 mg of FDI had no statistically significant impact on functional capacity or endothelial function, a trend to improved quality of life and no adverse effects of treatment.

Given the increasingly recognized importance and clinical implications of iron deficiency, this study adds further information. It should be recognized that the benefit of IV iron may be dose-related and 1000 mg may be insufficient to produce the necessary effects that are seen in patients with heart failure. This has been noted in the recent NIMO study (27).

At present the literature concerning functional benefits of IV iron in patients with iron deficiency and non-dialysis dependent CKD disease is limited, based upon small open label studies. Although the intervention in the present study did not lead to a significant increase in 6MWT, perhaps because the groups were not ideally matched at baseline and the overall trial population was small, there was a trend and numerical improvement that could be further assessed in a future larger trial.

Abbreviations

AiX Augmentation Index

ANCOVA analysis of covariance

ANOVA analysis of variance

BCP biochemical profile

BMI body mass index

CKD chronic kidney disease

CRP C reactive protein

ECG electrocardiogram

eCOPD exacerbation of chronic obstructive pulmonary disease

eGFR estimated glomerulular filtration rate

FBc full blood count

FDI ferric derisomaltose

Hb hemoglobin

IV intravenous

ID iron deficiency

KDIGO Kidney disease improving global outcomes

KD-QoL Kidney disease quality of life

LRTI lower respiratory tract infection

MedDRA Medical Dictionary for Regulatory Activities

MLHF Minnesota Living with heart failure

NHS National Health Service

NICE National Institute of Clinical Health and Care Excellence

NRES Northern Regional Ethics Service

NT-pro BNP N terminal pro brain natriuretic peptide

NYHA New York Heart Association functional classification

PWV pulse wave velocity

QoL quality of life

RLSS restless leg syndrome scale

6MWT six minute walk test

SD standard deviation

SF serum ferritin

TSAT transferrin saturation

uACR urinary albumin:creatinie ratio

UK United Kingdom

uPCR urinary protein:creatinie ratio

USA United States of America

UTI Urinary tract infection

Declarations

Ethical Approval and Consent to participate

The study was given a favourable opinion from the Northern Regional Ethics Service (NRES) Committee Yorkshire & The Humber - Leeds East, UK), approval reference number 10/H1306/40. Study participants had all details explained to them in writing and in person before giving informed consent.

Consent for publication

Neither this manuscript nor substantial parts of it are under consideration for publication elsewhere, have been published nor made available elsewhere in a manner that could be construed as a prior or duplicate publication of the same content. Otherwise not applicable.

Availability of supporting data

All data that is anonymized will be available from Hull University Teaching Hospitals NHS Trust with the relevant permissions and agreement of the Research and Development Committee of Hull University Teaching Hospitals NHS Trust.

Competing interests

VA declare no conflicts of interest. SB, IM and PK have received honorarium for lectures, attended expert opinion committees and received educational funds to attend International Nephrology meetings from Pharmacosmos A/S and Vifor Pharma.

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Authors' contributions

The initial draft of the manuscript was written by the first author and revised by all the authors. No medical writing assistance was provided. The authors had access to the final blinded trial results and unblinded statistical analysis and take responsibility for the accuracy and completeness of the data, for the fidelity of the trial to the protocol, and for the decision to submit the manuscript for publication.

VA assessed the statistical plan; Sunil Bhandari (SB) (Chief Investigator) participated in all aspects of the study, obtained funding for the study, and critically revised the manuscript. IM and PK contributed to the design of the study and reviewed the drafts of the manuscript and provided editing. The order of

authorship has been a joint decision of the co-authors based on substantial contribution to conception and design, execution, analysis, and interpretation of data. AL maintained the database. **All authors have read and approved the manuscript**.

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Figures

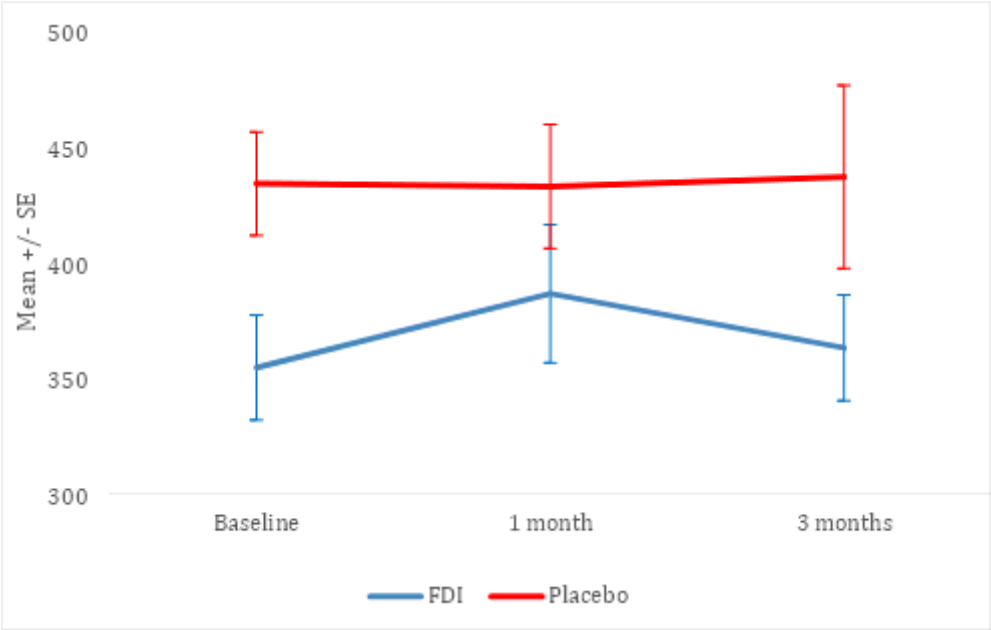

Figure 1

Mean (SE) 6-minute walk test (6-MWT) at baseline, 1 and 3 months in the Ferric Derisomaltose (FDI) and placebo arms.

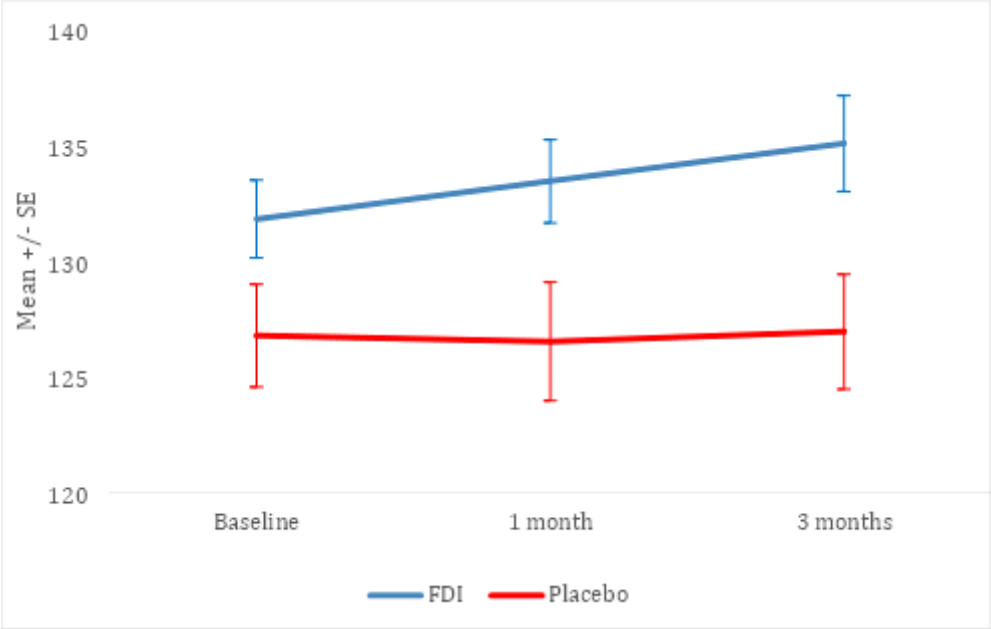

Figure 2

Mean (SE) of Hemoglobin (Hb) for IV iron (Ferric Derisomaltose) versus IV placebo at baseline, 1 month and 3 months.

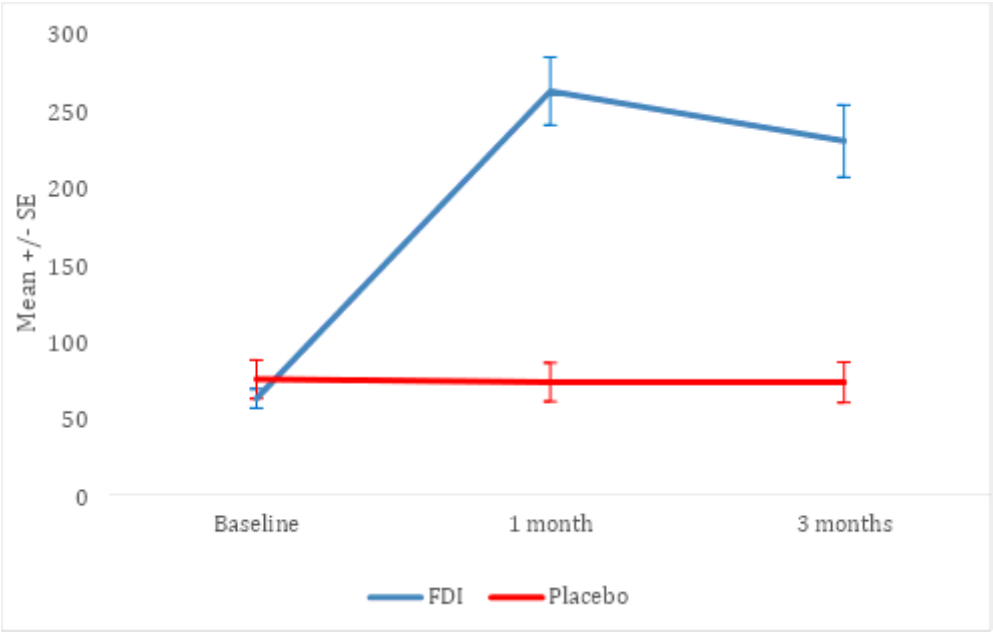

Figure 3

Mean (SE) of Hematinics – serum ferritin for IV iron (Ferric Derisomaltose) versus IV placebo at baseline, 1 month and 3 months.

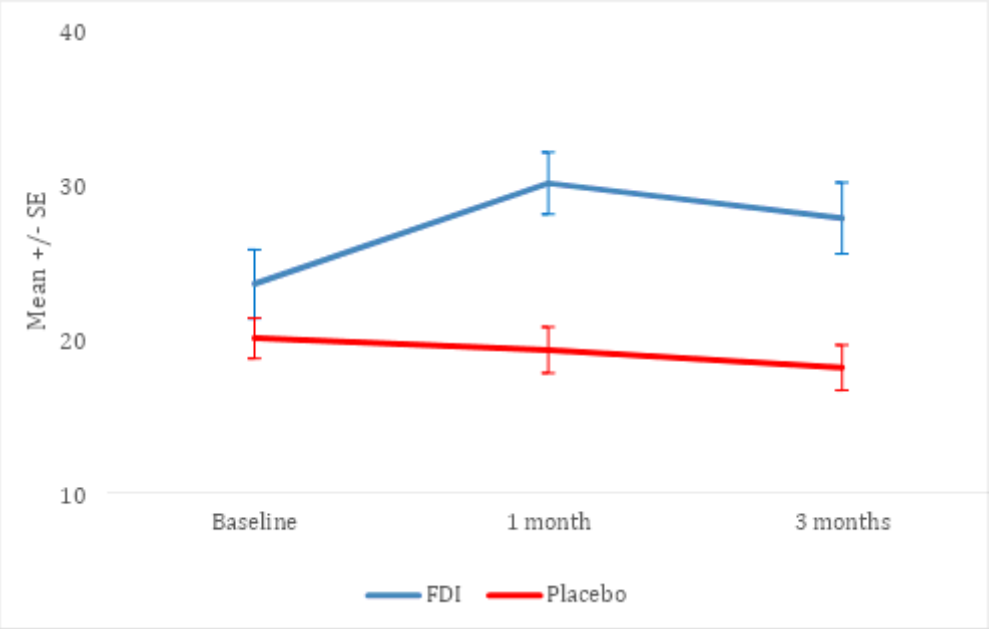

Figure 4

Mean (SE) of Hematinics –transferrin saturation (TSAT) for IV iron (Ferric Derisomaltose) versus IV placebo at baseline, 1 month and 3 months.

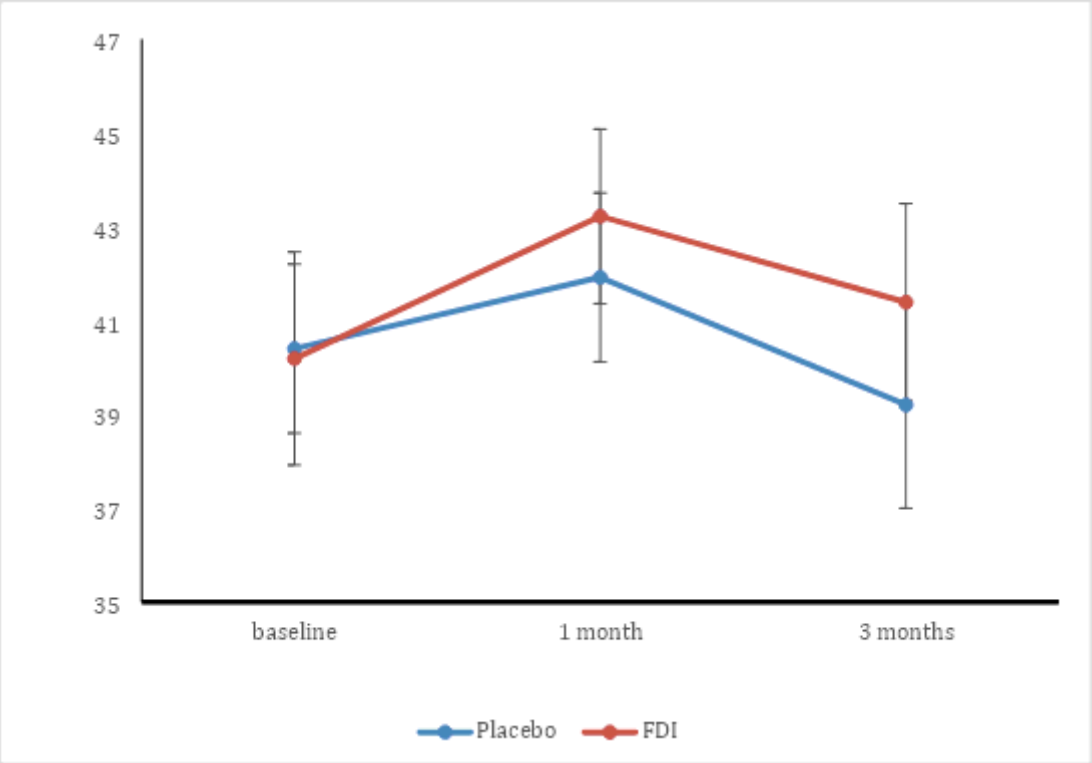

Figure 5

Mean (SE) for Kidney Disease Quality of life – Short Form-36 (KD-Qol SF-36) questionnaire (values are Z transformed and normalised values for component summary measure of Physical and Mental Health) for IV iron (Ferric Derisomaltose) versus IV placebo at baseline, 1 month and 3 months.

Supplementary Files

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