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FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia

Iain C. Macdougall[1], Andreas H. Bock[2], Fernando Carrera[3], Kai-Uwe Eckardt[4], Carlo Gaillard[5], David Van Wyck[6], Bernard Roubert[7], Jacqueline G. Nolen[7], Simon D. Roger[8] on behalf of the FIND-CKD Study Investigators[†]

[1]Department of Renal Medicine, King's College Hospital, Denmark Hill, London SE5 9RS, UK, [2]Department of Nephrology, Kantonsspital Aarau, Aarau, Switzerland, [3]Eurodial, DaVita, Leiria, Portugal, [4]Department of Nephrology and Hypertension, University of Erlangen-Nürnberg, Erlangen, Germany, [5]Department of Nephrology, University Medical Centre Groningen, University of Groningen, Groningen, the Netherlands, [6]DaVita Healthcare Partners Inc., Denver, CO, USA, [7]Vifor Pharma, Glattbrugg, Switzerland and [8]Renal Research, Gosford, NSW, Australia

Correspondence and offprint requests to: Iain C. Macdougall; E-mail: iain.macdougall@nhs.net
[†]Members of the Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease (FIND-CKD) study group are listed in Supplementary data, Appendix 1.

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ABSTRACT

Background. The optimal iron therapy regimen in patients with non-dialysis-dependent chronic kidney disease (CKD) is unknown.

Methods. Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease (FIND-CKD) was a 56-week, open-label, multicentre, prospective and randomized study of 626 patients with non-dialysis-dependent CKD, anaemia and iron deficiency not receiving erythropoiesis-stimulating agents (ESAs). Patients were randomized (1:1:2) to intravenous (IV) ferric carboxymaltose (FCM), targeting a higher (400–600 μg/L) or lower (100–200 μg/L) ferritin or oral iron therapy. The primary end point was time to initiation of other anaemia management (ESA, other iron therapy or blood transfusion) or haemoglobin (Hb) trigger of two consecutive values <10 g/dL during Weeks 8–52.

Results. The primary end point occurred in 36 patients (23.5%), 49 patients (32.2%) and 98 patients (31.8%) in the high-ferritin FCM, low-ferritin FCM and oral iron groups, respectively [hazard ratio (HR): 0.65; 95% confidence interval (CI): 0.44–0.95; P = 0.026 for high-ferritin FCM versus oral iron]. The increase in Hb was greater with high-ferritin FCM versus oral iron (P = 0.014) and a greater proportion of patients achieved an Hb increase ≥1 g/dL with high-ferritin FCM versus oral iron (HR: 2.04; 95% CI: 1.52–2.72; P < 0.001). Rates of adverse events and serious adverse events were similar in all groups.

Conclusions. Compared with oral iron, IV FCM targeting a ferritin of 400–600 μg/L quickly reached and maintained Hb level, and delayed and/or reduced the need for other anaemia management including ESAs. Within the limitations of this trial, no renal toxicity was observed, with no difference in cardiovascular or infectious events.

ClinicalTrials.gov number. NCT00994318.

Keywords: anaemia, chronic kidney disease

INTRODUCTION

For the last 25 years, erythropoiesis-stimulating agents (ESAs) and iron therapy have been the mainstay of anaemia management in patients with chronic kidney disease (CKD), while blood transfusions were only used when these therapies failed or when there was an urgent clinical need. ESAs have been shown to be highly effective in ameliorating anaemia in this setting [1]. However, large randomized controlled trials in patients with CKD either non-dialysed or on dialysis have shown that attempts to normalize haemoglobin (Hb) with ESAs are associated with no benefit for cardiovascular events or mortality, and an increased risk of stroke, venous thromboembolism and possibly death [2–6].

Secondary analyses of these trials indicated that these risks may be particularly prevalent in patients who are relatively unresponsive to highdosages of ESAs [7–9]. As a consequence, the prescription and dosage of ESAs have decreased, the number of blood transfusions has increased and—since iron deficiency is one of the main causes of hyporesponsiveness to ESAs—the use of iron therapy in patients with CKD, has increased significantly [10, 11]. However, in non-dialysis-dependent CKD patients with anaemia and/or iron deficiency, intravenous (IV) iron therapy remains far less widely utilized than in the dialysis population [12].

In patients receiving haemodialysis, IV iron has been shown to be significantly more effective than oral iron for replenishing depleted iron stores, improving Hb levels and reducing dosage requirements for ESAs [13–18]. However, in patients with non-dialysis-dependent CKD, the evidence base supporting optimal iron management is notably inadequate, as demonstrated by both a recent meta-analysis of oral versus IV iron in this patient population which included only six studies [19] and a Cochrane review, which included 10 studies [20] of relatively small size and short duration. Both these reports [19, 20], as well as the Kidney Disease: Improving Global Outcomes Clinical Practice Guideline for Anemia in Chronic Kidney Disease [1], stress the need for more robust clinical trials with longer follow-up in patients with non-dialysis-dependent CKD.

The Ferinject® assessment in patients with Iron deficiency anaemia and Non-Dialysis-dependent Chronic Kidney Disease (FIND-CKD) study assessed the 12-month efficacy and safety of IV ferric carboxymaltose (FCM) compared with oral iron to delay and/or reduce use of ESAs or other anaemia management options in patients with non-dialysis-dependent CKD, anaemia and iron deficiency not receiving an ESA. Iron therapy based on different ferritin targets has not been previously studied, therefore, two different treatment strategies were assessed using a dosing schema of IV FCM that was adjusted to achieve and maintain ferritin target levels that were either higher (400–600 μg/L) or lower (100–200 μg/L).

MATERIALS AND METHODS

Trial design and oversight

FIND-CKD was a 56-week, open-label, multicentre, prospective, randomized and three-arm study (ClinicalTrials.gov NCT00994318). Patients were randomized at 193 nephrology centres in 20 countries. The study design has been published previously (Supplementary data, Figure S1) [21]. Additional details of the methodology are provided in Appendix 2.

Recruitment

All inclusion and exclusion criteria are shown in Supplementary data, Table S1. Adult (≥18 years) patients with non-dialysis-dependent CKD were eligible if (i) at least one Hb level was between 9 and 11 g/dL within 4 weeks of randomization; (ii) any ferritin level was <100 or <200 μg/L with transferrin saturation (TSAT) <20%, within 4 weeks of randomization; (iii) estimated glomerular filtration rate (eGFR) was ≤60 mL/min/1.73 m^2 [Modification of Diet in Renal Disease-4 (MDRD-4) equation [22]], the rate of eGFR loss was ≤12 mL/min/1.73 m^2/year and predicted eGFR at 12 months was ≥15 mL/min/1.73 m^2; and (iv) no ESA had been administered within 4 months of randomization. Key exclusion criteria included anaemia due to reasons other than iron deficiency, documented history of discontinuing oral iron products due to significant gastrointestinal distress, known active infection, C-reactive protein >20 mg/L, overt bleeding, active malignancy, chronic liver disease and concomitant New York Heart Association Class IV heart failure.

Randomization

Eligible patients were randomized via a central interactive voice-response system in a 1:1:2 ratio (high-ferritin FCM: low-ferritin FCM: oral iron), with randomization blocks distributed by country.

Study therapy and anaemia management

FCM dose (Ferinject®, Vifor International, St Gallen, Switzerland) in the high-ferritin and low-ferritin FCM groups was adjusted to target a ferritin level of 400–600 and 100–200 μg/L, respectively (Supplementary data, Figure S2). An initial single dose was administered on Day 0: 1000 mg iron as FCM in the high-ferritin FCM group (500 mg iron on Days 0 and 7 in patients weighing ≤66 kg) and 200 mg iron as FCM in the low-ferritin FCM group if ferritin was <100 μg/L. During Weeks 4–48, FCM was administered every 4 weeks in the high-ferritin FCM group at a dose of 500 mg iron if ferritin was in the range 200 to <400 μg/L, and at a dose of 1000 mg iron if ferritin was <200 μg/L, and in the low-ferritin FCM group at a dose of 200 mg iron if ferritin was <100 μg/L. In both groups, dosing was withheld if TSAT was ≥40%. FCM was provided as 10 mL vials containing 500 mg iron per vial or 2 mL vials containing 100 mg iron per vial. Oral iron therapy consisted of commercially available ferrous sulphate at a dose of 100 mg iron twice daily to Week 52. Ferrous sulphate was supplied by Vifor Pharma (Plastufer® 100 mg capsules, Haupt Pharma Münster GmbH and Valeant Pharmaceuticals Germany GmbH). Returned unused oral iron capsules at each visit were counted to assess compliance.

During the first 8 weeks after randomization, patients were not to receive ESAs, blood transfusion or any anaemia therapy other than study drug unless there was an absolute requirement (e.g. severe or serious adverse reaction to study drug or otherwise unable to continue study drug, or rapid Hb drop requiring an ESA or transfusion, at the investigator's discretion). Subsequently, ESAs and other therapies were permitted according to local practice if the Hb was <10 g/dL. Use of ESAs was not permitted if the Hb level was ≥10 g/dL. Alternative iron therapy in patients with Hb >10 g/dL could be used but only when a patient was not able to comply with or tolerate the randomized treatment.

Primary and secondary end points

The primary end point of the study was time to initiation of other anaemia management, specified as ESAs, blood transfusion, use of an alternative iron therapy (i.e. product, dosing schedule or total dose different from study drug) or occurrence of an Hb trigger (two consecutive Hb values <10 g/dL on or after Week 8, without an increase of ≥0.5 g/dL between the two measurements, according to central laboratory

assessments). Secondary end points included percentage of patients requiring a blood transfusion; percentage of patients with an increase of Hb ≥1 g/dL; change in haematologic and iron indices from baseline to end of study; change in eGFR (MDRD-4 [22]) from baseline to end of study; percentage of patients requiring dialysis; percentage of patients discontinuing study drug due to intolerance; and change in health-related quality of life using the SF-36.

Statistical analysis

All patients who received at least one dose of randomized treatment (or according to the protocol were not treated due to ferritin level) and who attended at least one post-baseline visit were included in the intention-to-treat (ITT) population. All patients who received at least one dose of randomized treatment were included in the safety population.

The primary end point, time to initiation of other anaemia management or Hb trigger, was analyzed in the ITT population based on Kaplan–Meier survival analyses using the log-rank test to compare treatment arms. Patients who did not meet the end point were censored at the time of study completion or discontinuation. The hazard ratios (HRs) and associated 95% confidence intervals (CIs) from Cox proportional hazards modelling were also calculated as a supportive analysis. Three primary comparisons were made using a hierarchical step-down procedure to preserve the overall α level of 0.05, in the following order: (i) high-ferritin FCM versus oral iron, (ii) high-ferritin FCM versus low-ferritin FCM and (iii) low-ferritin FCM versus oral iron.

All other analyses were exploratory. For continuous secondary end points, either analysis of variance or analysis of covariance models were used, implementing repeated measures procedure where appropriate, and including treatment group, age, baseline Hb and/or baseline ferritin as covariates. For non-continuous end points (e.g. blood transfusion, requirement for dialysis), survival curves and logistic regressions were performed and odds ratios were used to compare treatment groups. The statistical analysis plan specified that analyses of haematological values and iron parameters (e.g. Hb, ferritin, TSAT), adverse events and serious adverse events were only for assessments up to the point at which another anaemia therapy was initiated and/or the randomized study medication was discontinued. No adjustment was made for testing multiple secondary outcomes.

All statistical analyses were performed using SAS Version 9.3 (SAS Institute Inc. SAS/STAT, Cary, NC).

RESULTS

Study population

From December 2009 to January 2012, 626 patients from 193 sites in 20 countries were randomized (Figure 1). The study was completed by 519 patients (82.9%). The most frequent reasons for discontinuation were patient withdrawal or death (12.9% in the FCM treatment arms versus 21.1% in the oral iron arm). The groups were well balanced with respect to demographic and baseline characteristics, with no clinically significant between-group differences (Table 1).

Treatment

The mean (SD) cumulative dose of FCM before initiation of any other anaemia therapy was 2685 (978) mg iron in the high-ferritin group and 1040 (618) mg iron in the low-ferritin group (with corresponding median values of 2500 and 1000 mg iron, respectively). The mean (SD) number of FCM injections required to reach and maintain the target ferritin was 4.0 (1.7) (range 1–10) and 4.8 (3.1) (range 1–14) in the high-ferritin and low-ferritin groups, respectively. In the high-ferritin group, patients received either 1000 or 500 mg iron to maintain a ferritin of 400–600 μg/L. In the low-ferritin group, the majority of patients received 200 mg iron to maintain a ferritin of 100–200 μg/L. The proportion of patients requiring an injection of FCM decreased progressively over time (Supplementary data, Figure S3). Non-adherence (<80% of prescribed study drug dose) was 16.4% in the oral iron treatment group and ≤2% in each of the FCM treatment groups.

Primary end point

Time to initiation of other anaemia management or occurrence of an Hb trigger (two consecutive Hb values <10 g/dL during Weeks 8–52) as assessed by Kaplan–Meier survival analysis was significantly different between the high-ferritin FCM group versus oral iron (HR: 0.65; 95% CI: 0.44–0.95; P = 0.026). The primary end point occurred in 36 patients (23.5%), 49 patients (32.2%) and 98 patients (31.8%) in the high-ferritin FCM, low-ferritin FCM and oral iron groups, respectively. Assessing the effectiveness of high-ferritin FCM versus oral iron, the number needed to treat to prevent either the initiation of other anaemia management or occurrence of an Hb trigger was 12.

The next comparison in the pre-defined hierarchical step-down procedure demonstrated no significant difference between the high-ferritin and low-ferritin FCM treatment arms (HR: 0.68; 95% CI: 0.45–1.058; P = 0.082). In a pre-specified sensitivity analysis, the primary end point was assessed based on locally measured Hb levels, which were used by investigators to make immediate anaemia management decisions. This additional analysis confirmed the primary analysis result that the high-ferritin FCM group was less likely than the oral iron group to require other anaemia treatment or reach the Hb trigger (HR: 0.62; 95% CI: 0.43–0.88; P = 0.008) (Table 2).

Overall, other anaemia management (118 events) comprising ESA therapy (58 events), blood transfusion (28 events), other iron therapy (25 events) or a combination of therapies (7 events) was the most commonly reported first event contributing to the primary end point, followed by Hb trigger (65 events). While ESA alone was the most common first alternative therapy used across all three treatment groups (10.5, 11.8 and 7.8% of patients in the high-ferritin, low-ferritin and oral iron groups, respectively) the oral iron group tended to receive other iron therapy as the first alternative anaemia therapy more often (6.5%) compared with either the high- or low-ferritin FCM arms (0 and 3.3%, respectively) (Table 2).

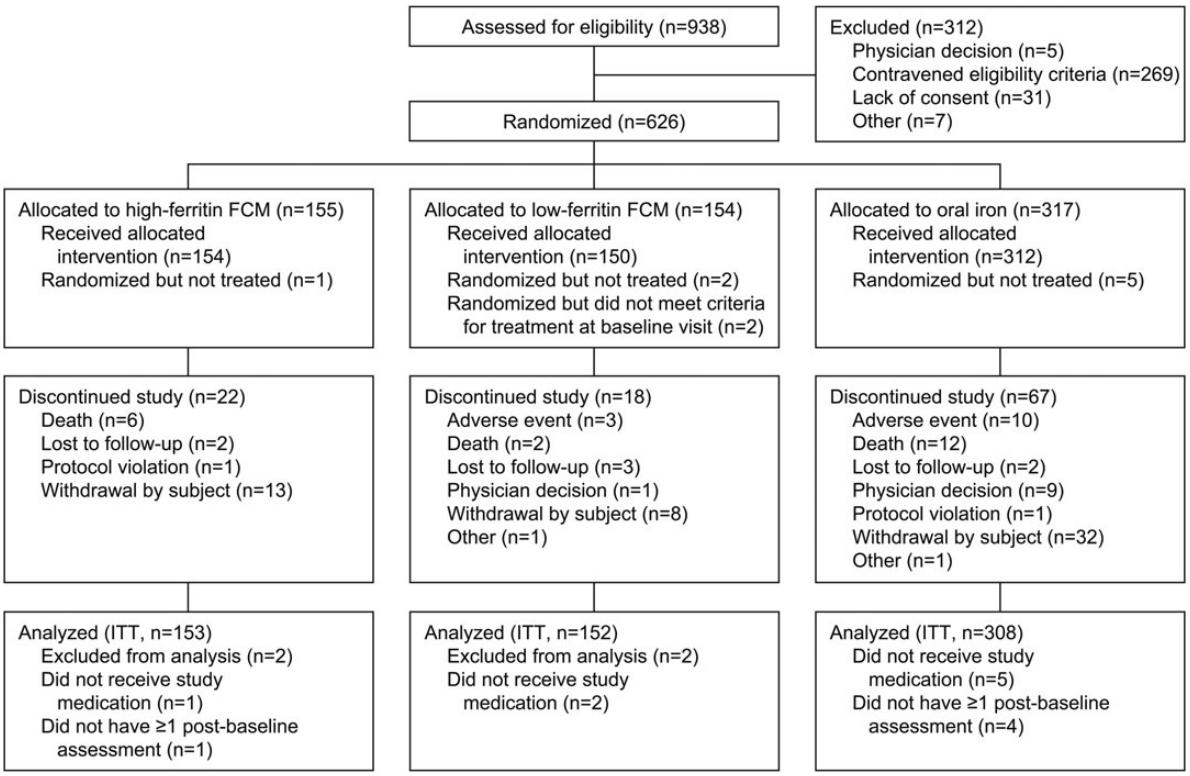

FIGURE 1: Enrolment and outcomes. The ITT population comprised all patients who received at least one dose of randomized treatment, or according to the protocol were not treated due to ferritin level, and attended at least one post-baseline visit. The safety population included all patients who received at least one dose of randomized treatment, and included 154 patients in the high-ferritin FCM group, 150 patients in the low-ferritin FCM group and 312 patients in the oral iron group. Two patients randomized to the low-ferritin FCM group met the eligibility requirements at screening but did not require FCM during the study according to the protocol-specified criteria for ferritin. These two patients were included in the ITT population but excluded from the safety population.

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Secondary end points

The requirement for blood transfusion was low during the course of the study and similar between treatment groups (Table 2).

All three groups showed an increase in Hb of 0.9–1.4 g/dL [least squares (LS) mean] from baseline to Month 12 without ESA (Table 2). The increase in LS mean Hb level in the high-ferritin FCM group versus the oral iron group was significantly greater from baseline to Month 12 ($P = 0.014$) (Table 2), and to all other time points (all $P < 0.05$, Figure 2B). In addition, the haematological response was faster (Figure 2B). The proportion of patients achieving an increase in Hb level ≥1 g/dL was 56.9, 34.2 and 32.1% in the high-ferritin FCM, low-ferritin FCM and oral iron groups, respectively. Patients in the high-ferritin FCM group were more likely to achieve an increase in Hb ≥1 g/dL compared with patients in either the low-ferritin FCM group (HR: 2.11; 95% CI: 1.49–2.98; $P < 0.001$) or oral iron group (HR: 2.04; 95% CI: 1.52–2.72; $P < 0.001$). The LS mean (SE) ferritin level at Month 12 was 503 (11) µg/L in the high-ferritin FCM group, the mid-point of the target range (400–600 µg/L) (Table 2, Figure 2C). LS mean (SE) TSAT level at Month 12 was similar in the high-ferritin FCM group and the oral iron group, with the lowest value observed in the low-ferritin FCM group (Table 2 and Figure 2D). eGFR was similar in all three treatment groups at baseline and at Month 12, with no marked change in renal function in any group during the study (Table 2). In total, 16 patients (2.6%) progressed to dialysis by Month 12, with no difference between groups.

Overall patient-reported quality of life outcomes, as measured by SF-36, did not show a statistically significant difference by treatment assignment.

Safety

A similar proportion of patients in each group had at least one adverse event during the study prior to the initiation of other anaemia management or occurrence of Hb trigger or discontinuation from study (high-ferritin FCM 81.8%, low-ferritin FCM 86.0% and oral iron 81.7%). The most common adverse events were peripheral oedema, hypertension, urinary tract infection and back pain in the FCM treatment groups (Table 3). In the oral iron group, diarrhoea, constipation, hypertension and peripheral oedema were the most commonly reported adverse events. Of the adverse events reported, 14.3, 15.3 and 28.5% were considered treatment related in the high-ferritin FCM, low-ferritin FCM and oral iron groups, respectively. Two patients in the low-ferritin FCM group experienced a drug hypersensitivity reaction, one of which was graded mild and the other graded moderate in severity by the investigator. Both led to withdrawal of study drug but neither case required treatment nor hospitalization, and there were no adverse sequelae. The mean serum phosphate level decreased by 0.18

Table 1. Baseline demographics and characteristics of patients in the ITT population according to study treatment arm[a]

	High-ferritin FCM (*n* = 153)	Low-ferritin FCM (*n* = 152)	Oral iron (*n* = 308)
Age (years)	69.5 (12.6)	68.2 (13.3)	69.3 (13.4)
Age >75 years, *n* (%)	54 (35.3)	54 (35.3)	121 (39.3)
Female gender, *n* (%)	91 (59.5)	98 (64.5)	192 (62.3)
Race, *n* (%)			
White	149 (97.4)	144 (94.7)	291 (94.5)
Black	2 (1.3)	5 (3.3)	7 (2.3)
Asian	2 (1.3)	3 (2.0)	9 (2.9)
Body mass index (kg/m^2)	29.7 (6.6)	29.9 (6.0)	29.1 (5.9)
History of diabetes, *n* (%)	88 (57.5)	97 (63.8)	195 (63.3)
eGFR (mL/min/1.73 m^2)[b]			
Mean (SD)	32.8 (11.7)	31.5 (10.7)	32.3 (11.6)
eGFR ≥60, *n* (%)	2 (1.3)	1 (0.7)	3 (1.0)
eGFR 30 to <60, *n* (%)	86 (56.2)	79 (52.0)	167 (54.2)
eGFR 15 to <30, *n* (%)	62 (40.5)	69 (45.4)	128 (41.6)
eGFR <15, *n* (%)	3 (2.0)	3 (2.0)	10 (3.2)
Endogenous erythropoietin (mIU/mL)[c]			
Mean (SD)	28.2 (30.0)	27.1 (25.0)	31.4 (91.5)
Median (range)	20.3 (3.6, 272.0)	20.7 (4.9, 187.0)	19.1 (3.8, 1531.0)
Hb (g/dL)[c]			
Mean (SD)	10.3 (0.7)	10.5 (0.8)	10.4 (0.7)
<10, *n* (%)	43 (28.1)	32 (21.1)	73 (23.7)
≥10	106 (69.3)	112 (73.7)	229 (74.4)
Ferritin (μg/L)[c]			
Mean (SD)	57.7 (48.1)	56.4 (49.2)	57.3 (42.4)
<100, *n* (%)	123 (80.4)	124 (81.6)	251 (81.5)
≥100, *n* (%)	23 (15.0)	22 (14.5)	41 (13.3)
TSAT (%)[d]			
Mean (SD)	16.2 (16.7)	16.1 (8.3)	15.5 (7.6)
<20, *n* (%)	112 (73.2)	114 (75.0)	215 (69.8)
≥20, *n* (%)	32 (20.9)	34 (22.4)	78 (25.3)
C-reactive protein (mg/L)[d]			
Mean (SD)	6.7 (11.3)	6.2 (9.1)	5.2 (6.1)
Median (range)	3.5 (0.0, 99.7)	4.0 (0.0, 94.0)	3.5 (0.0, 59.1)
Hepcidin (nmol/L)[c,e]			
Mean (SD)	1.43 (1.24)	2.60 (2.23)	2.30 (2.01)
Median (range)	1.15 (0.02, 3.54)	2.11 (0.12, 9.99)	1.87 (0.05, 7.63)

eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; Hb, haemoglobin; TSAT, transferrin saturation.
[a]Continuous variables are shown as mean (SD) unless otherwise stated.
[b]Estimated by MDRD-4 equation [22] at local laboratory.
[c]Measured at central laboratory.
[d]Measured at local laboratory.
[e]Data available in 17 high-ferritin FCM patients, 17 low-ferritin FCM patients and 35 oral iron patients.

mmol/L at Week 4 from a baseline value of 1.22 (0.2) mmol/L in the high-ferritin FCM group, but returned to baseline by Month 12 (Supplementary data, Figure S4). There were no cases of hypophosphataemia reported as adverse events. Serious adverse events were reported in 25.3, 24.0 and 18.9% of patients in the high-ferritin FCM, low-ferritin FCM and oral iron groups, respectively. None of the serious adverse events in the FCM treatment groups and one (0.3%) in the oral iron group were considered treatment related. Benign or malignant neoplasms were reported in 12 patients (7.8%) in the high-ferritin FCM arm, five patients (3.3%) in the low-ferritin FCM arm and eight patients (2.6%) in the oral iron group. No type of neoplasm occurred in more than one patient in any group except for basal cell carcinoma (three in the high-ferritin FCM arm) and multiple myeloma (two in the oral iron arm). The most commonly reported serious adverse events by organ class were cardiac disorders and infections and were similar between treatment groups (Table 3).

Study drug was discontinued due to intolerance in one patient (0.7%) in the high-ferritin FCM group, two patients (1.3%) in the low-ferritin FCM group and 23 patients in the oral iron group (7.5%) (HR: 0.08; 95% CI: 0.01–0.62; P = 0.002 for high-ferritin FCM versus oral iron). Of the 23 patients who discontinued oral iron therapy, 15 stopped treatment before Week 8 (65.2%). Adverse events leading to discontinuation from study occurred in five (3.2%) patients in the high-ferritin FCM group, seven (4.7%) in the low-ferritin FCM group and 42 (13.5%) in the oral iron group. Gastrointestinal disorders did not lead to study drug discontinuation in any patients receiving FCM but contributed to intolerance in 23 patients receiving oral iron (7.5%) who discontinued treatment.

During the 56-week study period, 25 patients died (4.1%). None of the deaths was assessed by the investigator as related to study drug. Twelve deaths occurred prior to initiation of other anaemia treatment, occurrence of the Hb trigger or discontinuation of study drug and 13 deaths occurred

Table 2. Primary end point and selected secondary end points (ITT population)[a]

	High-ferritin FCM (n = 153)	Low-ferritin FCM (n = 152)	Oral iron (n = 308)
Primary end point			
Time to initiation of other anaemia management or Hb trigger (central monitoring)[b,e]			
n (%)	36 (23.5)	49 (32.2)	98 (31.8)
HR (95% CI)[c]	Reference	0.68 (0.45, 1.05)	0.65 (0.44, 0.95)
P-value (log-rank)	Reference	0.082	0.026
Events contributing to primary end point			
Hb trigger[b]	10 (6.5)	19 (12.5)	36 (11.7)
ESA only	16 (10.5)	18 (11.8)	24 (7.8)
Other iron therapy only	0	5 (3.3)	20 (6.5)
ESA and iron therapy	0	2 (1.3)	2 (0.6)
Transfusion	9 (5.9)	5 (3.3)	14 (4.5)
ESA and transfusion	1 (0.7)	0	2 (0.6)
Primary end point			
Time to initiation of other anaemia management or Hb trigger (local monitoring)[b,d,e]			
n (%)	40 (26.1)	55 (36.2)	115 (37.3)
HR (95% CI)[c]	Reference	0.68 (0.45, 1.03)	0.62 (0.43, 0.88)
P-value (log-rank)	Reference	0.064	0.008
Secondary end points			
Blood transfusion			
n (%)	11 (7.2)	11 (7.2)	26 (8.4)
Odds ratio (95% CI)	0.89 (0.42, 1.88)	0.97 (0.46, 2.04)	Reference
P-value	0.77	0.94	Reference
Time to Hb increase ≥1 g/dL[e,f,g]			
n (%)	87 (56.9)	52 (34.2)	99 (32.1)
HR (95% CI)	Reference	2.11 (1.49, 2.98)	2.04 (1.52, 2.72)
P-value (log-rank)	Reference	<0.001	<0.001
Hb, LS mean (SE) (g/dL)[f,h]			
Baseline	10.1 (0.1)	10.2 (0.1)	10.2 (0.1)
Month 12	12.0 (0.1)	11.5 (1.1)	11.5 (0.1)
Change from baseline	1.4 (0.1)	0.9 (0.1)	1.0 (0.1)
P-value (change from baseline to Month 12 versus oral iron[i])	0.014	0.26	Reference
Ferritin, LS mean (SE) (μg/L)[f,h]			
Baseline	54 (9)	48 (9)	53 (6)
Month 12	503 (11)	125 (11)	184 (8)
Change from baseline	451 (10)	81 (11)	137 (8)
P-value (change from baseline to Month 12 versus oral iron[i])	<0.001	<0.001	Reference
TSAT, LS mean (SE) (%)[f,h]			
Baseline	16.2 (1.0)	16.1 (1.0)	15.5 (0.7)
Month 12	31.2 (1.3)	24.2 (1.3)	28.6 (1.0)
Change from baseline	15.8 (1.3)	8.5 (1.3)	13.8 (1.0)
P-value (change from baseline to Month 12 versus oral iron[i])	0.20	0.001	Reference
eGFR, LS mean (SE) (mL/min/1.73 m^2)[j]			
Baseline	32.1 (1.1)	31.8 (1.1)	33.2 (0.8)
Month 12	35.3 (1.4)	31.1 (1.4)	33.7 (1.0)
Change from baseline	0.4 (0.8)	−1.6 (0.8)	−1.1 (0.6)
P-value (change from baseline to Month 12 versus oral iron[i])	0.14	0.64	Reference
Requirement for dialysis			
n %	5 (3.3)	1 (0.7)	10 (3.2)
Odds ratio (95% CI)	1.01 (0.34, 3.00)	0.20 (0.03, 1.56)	Reference
P-value	0.99	0.12	Reference

eGFR, estimated glomerular filtration rate; FCM, ferric carboxymaltose; Hb, haemoglobin; LS, least squares; TSAT, transferrin saturation.
[a]Continuous variables are shown as mean (SD).
[b]Time to initiation of other anaemia management such as an ESA or transfusion, or an Hb trigger (two consecutive Hb values <10 g/dL on or after Week 8, without an increase of ≥0.5 g/dL between the two measurements).
[c]Proportional hazards modelling.
[d]Pre-specified sensitivity analysis.
[e]Kaplan–Meier estimates.
[f]Measured at local laboratory.
[g]Prior to first initiation of other anaemia management.
[h]Measurements were included up to the point at which other anaemia therapy was initiated and/or the randomized study medication was discontinued.
[i]Analysis of covariance analysis based on LS mean values.
[j]Estimated by MDRD-4 equation [22] at local laboratory.

subsequently. There were seven deaths (4.5%) in the high-ferritin FCM arm, three (2.0%) in the low-ferritin FCM arm and 15 (4.8%) in the oral iron arm. The average age of the patients who died was 74.6 years and the most frequently reported causes of death were cardiovascular events or respiratory infections.

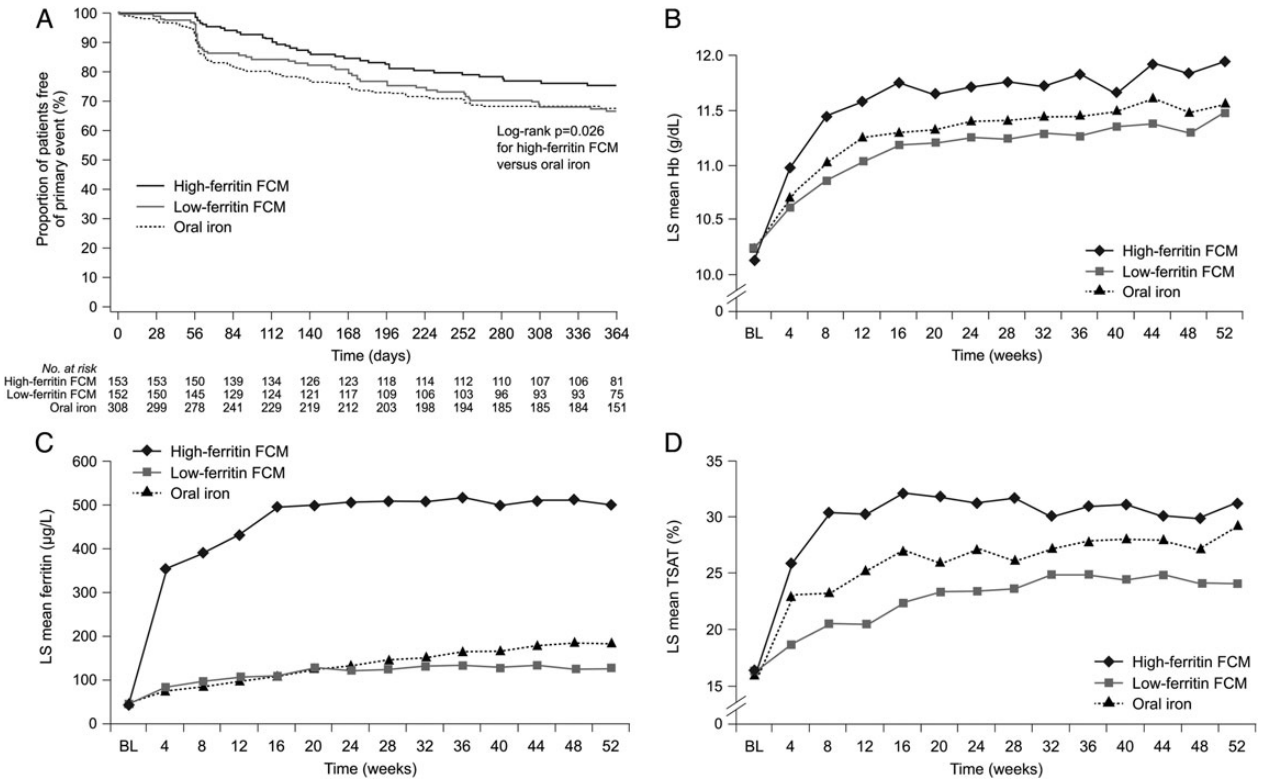

FIGURE 2: (**A**) Time to initiation of other anaemia management or Hb trigger (Kaplan–Meier estimates) and LS mean locally measured observed values over time for (**B**) Hb (**C**) ferritin and (**D**) TSAT according to treatment group (ITT population). Measurements of Hb, ferritin and TSAT were included up to the point at which other anaemia therapy was initiated (with or without cessation of randomized study drug) and/or the patient discontinued the study. BL, baseline; FCM, ferric carboxymaltose.

DISCUSSION

This randomized trial met its primary end point and showed that in patients with non-dialysis-dependent CKD, anaemia and iron deficiency not receiving an ESA, IV FCM targeting a ferritin of 400–600 µg/L is more effective than oral iron in delaying and/or reducing the requirement for an ESA, other anaemia management or the occurrence of two consecutive Hb levels <10 g/dL. There was no significant difference between the FCM treatment arms targeting a higher versus lower ferritin range. There was also no apparent difference between the low-ferritin FCM and oral iron groups, although no statistical analysis was performed to compare these two treatment arms, as per the hierarchical step-down procedure, which was predefined in the study protocol.

In the setting of this controlled trial, the use of blood transfusion was low and similar in all three treatment groups. Each group showed an increase in mean values for ferritin, TSAT and Hb from baseline to Month 12. Mean ferritin levels within the pre-specified target ranges were achieved and maintained in both of the FCM treatment arms. The mean increase in Hb prior to the initiation of other anaemia therapy in all three treatment groups was 0.9–1.4 g/dL. However, patients in the high-ferritin FCM group had a faster haematological response and were more likely to have an increase in Hb ≥1 g/dL.

Early iron dosing of 500–1000 mg in the high-ferritin FCM group successfully achieved and maintained the ferritin target with relatively few subsequent injections. No more than 25% of patients in the high-ferritin FCM group required an injection at any study visit after Month 4, whereas patients in the oral iron group were required to take one capsule twice daily for 12 months.

Overall, 21.1% of patients in the oral iron group discontinued the study compared with 14.2 and 11.7% in the high-ferritin and low-ferritin FCM arms, respectively. In addition, 23 patients in the oral iron group discontinued study drug due to intolerance (7.5%), and of these patients 65% discontinued within the first 8 weeks of the study.

Although previous studies in laboratory experiments, animal models and patients have raised concerns about possible nephrotoxicity of IV iron agents [23], no clinically relevant deterioration in renal function was observed in any of the treatment groups during this 12-month trial.

Potential other concerns that have been associated with IV iron therapy include hypersensitivity reactions, hypophosphataemia, oxidative stress (which may increase the risk of cardiovascular events) and exacerbation of infection. In the current study, two patients had a hypersensitivity reaction to IV iron therapy. The reactions were not severe and resolved spontaneously with no sequelae. There were no clinically significant hypophosphataemic episodes, although there was an early and transient decrease in the mean serum phosphate level in the high-ferritin FCM group. Markers of oxidative stress were not assessed in this study, but the incidence of cardiovascular events, deaths and infections was similar between treatment groups. We observed a numerically higher percentage of

Table 3. Adverse events and serious adverse events (safety population)

Event	High-ferritin FCM (n = 154)	Low-ferritin FCM (n = 150)	FCM total (n = 304)	Oral iron (n = 312)
Any adverse event, *n* (%)	126 (81.8)	129 (86.0)	255 (83.9)	255 (81.7)
Gastrointestinal disorders	32 (20.8)	38 (25.3)	70 (23.0)	128 (41.0)
Diarrhoea	15 (9.7)	11 (7.3)	26 (8.6)	45 (14.4)
Constipation	2 (1.3)	5 (3.3)	7 (2.3)	37 (11.9)
Nausea	9 (5.8)	7 (4.7)	16 (5.3)	15 (4.8)
Dyspepsia	2 (1.3)	3 (2.0)	5 (1.6)	17 (5.4)
Infections	51 (33.1)	51 (34.0)	102 (33.6)	95 (30.4)
Urinary tract infection	18 (11.7)	10 (6.7)	28 (9.2)	17 (5.4)
Nasopharyngitis	13 (8.4)	10 (6.7)	23 (7.6)	16 (5.1)
Influenza	4 (2.6)	8 (5.3)	12 (3.9)	7 (2.2)
General disorders and administrative site conditions	36 (23.4)	35 (23.3)	71 (23.4)	67 (21.5)
Peripheral oedema	21 (13.6)	21 (14.0)	42 (13.8)	29 (9.3)
Musculoskeletal and connective tissue disorders	35 (22.7)	42 (28.0)	77 (25.3)	56 (17.9)
Back pain	15 (9.7)	12 (8.0)	27 (8.9)	11 (3.5)
Arthralgia	10 (6.5)	7 (4.7)	17 (5.6)	15 (4.8)
Pain in extremity	2 (1.3)	8 (5.3)	10 (3.3)	15 (4.8)
Vascular disorders	33 (21.4)	26 (17.3)	59 (19.4)	52 (16.7)
Hypertension	21 (13.6)	14 (9.3)	35 (11.5)	32 (10.3)
Hypotension	8 (5.2)	4 (2.7)	12 (3.9)	5 (1.6)
Respiratory, thoracic and mediastinal disorders	19 (12.3)	27 (18.0)	46 (15.1)	41 (13.1)
Dyspnoea	7 (4.5)	11 (7.3)	18 (5.9)	11 (3.5)
Nervous system disorders	25 (16.2)	28 (18.7)	53 (17.4)	33 (10.6)
Dizziness	9 (5.8)	8 (5.3)	17 (5.6)	7 (2.2)
Headache	6 (3.9)	10 (6.7)	16 (5.3)	7 (2.2)
Blood and lymphatic system disorders	8 (5.2)	11 (7.3)	19 (6.3)	13 (4.2)
Anaemia	7 (4.5)	8 (5.3)	15 (4.9)	10 (3.2)
Serious adverse event, *n* (%)	39 (25.3)	36 (24.0)	75 (24.7)	59 (18.9)
Cardiac disorders	10 (6.5)	7 (4.7)	17 (5.6)	14 (4.5)
Acute myocardial infarction	2 (1.3)	0 (0)	2 (0.7)	4 (1.3)
Cardiac failure	1 (0.6)	0 (0)	1 (0.3)	3 (1.0)
Infections	6 (3.9)	5 (3.3)	11 (3.6)	12 (3.8)
Pneumonia	0 (0)	1 (0.7)	1 (0.3)	4 (1.3)
Injury, poisoning and procedural complications	4 (2.6)	3 (2.0)	7 (2.3)	8 (2.6)
Neoplasms (benign and malignant)	8 (5.2)	3 (2.0)	11 (3.6)	2 (0.6)
Gastrointestinal disorders	3 (1.9)	6 (4.0)	9 (3.0)	2 (0.6)
Nervous system disorders	2 (1.3)	1 (0.7)	3 (1.0)	6 (1.9)
Respiratory, thoracic and mediastinal disorders	1 (0.6)	2 (1.3)	3 (1.0)	6 (1.9)
Chronic obstructive pulmonary disease	0	2 (1.3)	2 (0.7)	2 (0.6)
Vascular disease	2 (1.3)	3 (2.0)	5 (1.6)	4 (1.3)

FCM, ferric carboxymaltose.

Listed are the most common adverse events according to body system (occurring in ≥10% of patients in any group) and as individual types of events (occurring in ≥5% of patients in any group). Serious adverse events are listed if they occurred in ≥1% of patients in any study group. Adverse events and serious adverse events are reported up to the point at which another anaemia therapy was initiated and/or the randomized study medication was discontinued.

benign and malignant neoplasms in the high-ferritin FCM arm as compared with the two other arms. However, the absolute numbers were small and there was no increase in any specific type of neoplasm. In addition, this trial was not powered to assess a safety end point, therefore, we cannot make any firm conclusions about the long-term risk : benefit ratio. Furthermore, this study does provide safety data over a 56-week period, which is considerably longer than previous trials of IV iron in patients with CKD that have frequently only followed patients for up to 8 weeks [24–28].

The study has several limitations. There was no placebo arm in the study, thus precluding a comparison of efficacy and safety between the interventions and no treatment. Moreover, an open-label study design was used so that both the physicians and patients were aware of the treatment allocation. Avoiding this would have required a double-blind, double-dummy design and at the time the study was being designed it was not considered ethically appropriate to administer placebo IV iron injections, potentially every 4 weeks for a year. The generalizability of improvements in Hb and iron status in the oral iron group to the wider non-dialysis-dependent CKD population may be limited for several reasons. The patients were predominantly white, had a low-inflammatory status (facilitating the absorption and utilization of oral iron) and showed a degree of tolerance and compliance with oral iron treatment that is unlikely to be matched in everyday clinical practice. In addition, patients were excluded who had a history of intolerance to oral iron prior to study entry. A further significant limitation is that we did not include more patient-centred outcome measurements.

In conclusion, patients with non-dialysis-dependent CKD, anaemia and iron deficiency may benefit from IV iron treatment targeting a higher ferritin level. Both IV and oral iron therapy were effective in increasing Hb, ferritin and TSAT

levels in this setting; however, FCM therapy with a higher ferritin target was shown to be superior to oral iron in delaying and/or reducing the requirement for other anaemia management or occurrence of an Hb trigger during the 12-month study, as well as producing a faster haematological response with a greater proportion of patients achieving an Hb increase of ≥1 g/dL. These results were achieved with relatively few FCM injections and despite selecting patients for inclusion in the study who might be expected to do well on oral iron therapy. High-ferritin FCM was well tolerated, with fewer treatment-related adverse events and study discontinuations versus oral iron and within the limitations of this trial, no renal toxicity and no increases in cardiovascular or infectious events were observed. These findings support current guidelines [1], which recommend a trial of iron therapy if an increase in Hb without ESA therapy is desired in patients with CKD, anaemia and iron deficiency. Furthermore, based on the findings in this study, targeting a higher ferritin level with IV FCM may contribute to improved anaemia management.

SUPPLEMENTARY DATA

Supplementary data are available online at http://ndt.oxfordjournals.org.

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AUTHORS' CONTRIBUTIONS

I.C.M., A.H.B., F.C., K-U.E., D.V.W. and S.D.R. contributed to the study design. I.C.M. and S.D.R. recruited patients and collected data during the study. I.C.M., A.H.B., F.C., K-U.E., C.G., D.V.W. and S.D.R. thoroughly reviewed the data and results. I.C.M. and S.D.R. developed the first draft of the manuscript, which was critically reviewed and revised by the other authors. B.R. provided biostatistical support. J.G.N. provided clinical support.

CONFLICT OF INTEREST STATEMENT

I.C.M. has received speakers' fees, honoraria and consultancy fees from several manufacturers of ESAs and IV iron, including Affymax, AMAG, Amgen, Ortho Biotech, Pharmacosmos, Hoffmann-La Roche, Takeda and Vifor Pharma. A.H.B. has received speaker's honoraria and consultancy fees from Amgen, Hoffmann-La Roche and Vifor Pharma. F. C. has no conflicts of interest to declare. K.-U.E. has received speaker's fees and consultancy fees from several manufacturers of ESAs and IV iron, including Affymax, Amgen, Bayer, Johnson & Johnson, Hoffmann-La Roche and Vifor Pharma. C.G. has received speakers' fees, honoraria and consultancy fees from several manufacturers of ESAs and IV iron, including Amgen, Pharmacosmos, Hoffmann-La Roche, Takeda and Vifor Pharma. D.V.W. is an employee and stockholder of DaVita Healthcare Partners, Inc. B.R. and J.G.N. are employees of Vifor Pharma. S.D.R. has received speakers' fees, honoraria and consultancy fees from several manufacturers of ESAs and IV iron, including Amgen, Hoffmann-La Roche, Janssen-Cilag, Novartis, Sandoz, Takeda and Vifor Pharma.

The results presented in this paper have not been published previously in whole or part, except in abstract format.

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ORIGINAL ARTICLE

Rituximab for minimal-change nephrotic syndrome in adulthood: predictive factors for response, long-term outcomes and tolerance

Joëlle Guitard[1,†], Anne-Laure Hebral[1,†], Fadi Fakhouri[2], Dominique Joly[3], Eric Daugas[4], Joseph Rivalan[5], Vincent Guigonis[6], Françis Ducret[7], Claire Presne[8], Yves Pirson[9], Maryvonne Hourmant[2], Jean-Claude Glachant[10], Benoit Vendrely[11], Olivier Moranne[12], Stanislas Faguer[1,†] and Dominique Chauveau[1,†]

[1]Département de Néphrologie et Transplantation d'organes, CHU Rangueil, Toulouse, France, [2]Service de Néphrologie et Transplantation rénale, CHU Hôtel-Dieu, Nantes, France, [3]Service de Néphrologie, CHU Necker Enfants Malades, AP-HP, Paris, France, [4]Service de Néphrologie et Transplantation, CHU Bichat, AP-HP, Paris, France, [5]Service de Néphrologie, CHU de Pontchaillou, Rennes, France, [6]Service de Néphrologie Pédiatrique, CHU Dupuytren, Limoges, France, [7]Service de Néphrologie, Centre Hospitalier Annecy - Genevois, Annecy, France, [8]Service de Néphrologie, CHU Amiens-Picardie, Amiens, France, [9]Service de Néphrologie, Cliniques Universitaires Saint-Luc, Bruxelles, Belgique, [10]Service de Néphrologie, Centre Hospitalier de Bourg-en-Bresse, Bourg-en-Bresse, France, [11]Service de Néphrologie, CHU Pellegrin, Bordeaux, France and [12]Service de Néphrologie et Transplantation rénale, CHU Pasteur, Nice, France

Correspondence and offprint requests to: Stanislas Faguer; E-mail: faguer.s@chu-toulouse.fr
[†]These authors contributed equally to this work.

ABSTRACT

Background. Minimal-change nephrotic syndrome (MCNS) is a common cause of steroid sensitive nephrotic syndrome (NS) with frequent relapse. Although steroids and calcineurin inhibitors (CNIs) are the cornerstone treatments, the use of rituximab (RTX), a monoclonal antibody targeting B cells, is an efficient and safe alternative in childhood.