ORIGINAL ARTICLE

Effectiveness and safety of ferric carboxymaltose therapy in peritoneal dialysis patients: an observational study

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ABSTRACT

Background. The efficacy of intravenous (IV) ferric carboxymaltose (FCM) has been demonstrated in haemodialysis and non-dialysis studies, but evidence is lacking in patients undergoing peritoneal dialysis (PD).

Methods. This multicentre, retrospective study evaluated the effectiveness and safety of FCM in patients on PD over 12 months. We retrospectively reviewed the electronic medical records of PD patients who initiated FCM treatment between 2014 and 2017 across seven Spanish centres.

Results. Ninety-one patients were included in the safety population (mean ± SD age 57.7 ± 15.0 years) and 70 in the efficacy population (mean age 50.9 ± 14.5 years). No hypersensitivity reaction, FCM discontinuation or dose adjustment due to a serious adverse event (SAE) was registered in the safety population. The most common non-SAEs reported were headache (four events), mild hypotension (three events) and hypertension (two events), among others. In the efficacy population ($n = 70$), 68.6% of patients achieved ferritin levels of 200–800 ng/mL, 78.4% achieved transferrin saturation (TSAT) >20%, and 62.8% achieved TSAT >20% and ferritin >200 ng/mL after 12 months of FCM initiation (P < 0.01). Haemoglobin (Hb) levels were maintained at >11 g/dL with a lower dose of darbepoetin throughout the follow-up. The sub-analysis of patients naïve to IV iron and with absolute or relative iron deficiency ($n = 51$) showed that 76.5% reached ferritin >200 ng/mL, 80.4% TSAT >20% and Hb increased (1.2 g/dL) after 4 months of FCM treatment (P < 0.01).

Conclusion. In this multicentre, retrospective, real-world study conducted in the PD population, FCM was effective, safe and easy to administer during routine clinical visits.

Keywords: anaemia, chronic kidney disease, ferric carboxymaltose, iron deficiency, peritoneal dialysis

INTRODUCTION

Anaemia and iron deficiency are common complications of chronic kidney disease (CKD). The prevalence of iron deficiency increases as renal function decreases, hindering the efficacy of erythropoiesis-stimulating agents (ESAs). The National health and nutritional examination survey (NHANES) study found a high prevalence (65%) of iron deficiency in patients with CKD Stages 3–5 [1], whereas the prevalence can reach 75% in peritoneal dialysis (PD) and even higher rates in haemodialysis (HD) [2]. Iron deficiency plays an important role in the development of anaemia in CKD, which is associated with increased morbidity and mortality, impaired quality of life, poor functional status and CKD progression [3, 4]. Hence, an association between iron deficiency and mortality has also been reported [5].

The Kidney Disease: Improving Global Outcomes (KDIGO) guideline recommends iron supplementation for patients with or without the concurrent administration of ESAs to increase haemoglobin (Hb) levels or decrease ESA doses, provided that ferritin is <500 ng/mL and transferrin saturation (TSAT) is <30% [4]. Iron therapies include intravenous (IV) and oral routes of administration, the latter being frequently associated with gastrointestinal side effects and poor compliance, as well as poor gastrointestinal absorption and availability in CKD. In a randomized, cross-over study, the intraperitoneal route was proven inefficient and was therefore not recommended in PD patients [6]. IV iron use is advisable as first-line treatment in patients on dialysis or after an unsuccessful oral iron trial in non-dialysis patients (ND-CKD). A recent meta-analysis demonstrated the efficacy and safety of IV compared with oral iron both in HD and ND-CKD settings, but none of the studies was conducted in the PD population [7]. The National Institute for Health and Care Excellence (NICE) guideline recommends IV iron formulations [such as ferric carboxymaltose (FCM)] that allow a high-dose low-frequency strategy for ND-CKD patients [8]. FCM is a stable, non-dextran iron formulation providing a rapid and efficient repletion of iron stores [9, 10] with a controlled delivery of high iron doses into target tissues. In addition, the European Society of Cardiology guideline goes beyond the nephrologist perspective and recommends the use of FCM in patients with heart failure with reduced ejection fraction and iron deficiency with or without anaemia [11], given the positive results observed in randomized clinical trials [12, 13].

The efficacy of IV iron therapy at correcting Hb and iron indices has been proven in different settings including ND-CKD [14–16] and HD [17]. However, the evidence is weak in patients undergoing PD since a limited number of small, non-controlled and short-term studies are available [18–26]. Different reasons can plausibly explain the lack of evidence for PD. First, the proportion of patients that initiate PD in Europe is lower (∼14%) than that for HD and varies widely among different countries (2–33%) [27]. In Spain, these figures are similar, but we find other causes: PD units are small, and patients remain on PD during shorter periods (∼2 years) than on HD. This is because the mortality is low, and kidney transplantation is the first cause of PD withdrawal [28]. Lastly, companies seem to have little interest in investing in research in this area. All these reasons present a challenging scenario for conducting well-designed, controlled studies that may guide clinical decisions.

This was a retrospective observational study conducted by the Spanish working group *Grupo Centro de Diálisis Peritoneal* (GCDP) to describe the procedures, effectiveness and safety of IV FCM treatment in a real-world setting of iron-deficient PD patients.

MATERIALS AND METHODS

Study design

This multicentre, retrospective, observational study assessed the effectiveness and safety of PD patients initiating FCM treatment between 2014 and 2017 across seven Spanish centres of the GCDP working group. The study retrospectively collected data from the GCDP database, which systematically includes demographic and clinical information from the electronic medical records of patients receiving PD [29]. Data related to FCM administration, clinical variables and adverse events (AEs) were retrospectively retrieved at baseline (before FCM initiation) and for up to 12 months (at Months 2, 4, 6 and 12).

The study adhered to the principles of the Declaration of Helsinki and was approved by the Independent Ethics Committees of the University Hospital Puerta del Hierro (Madrid, Spain). Written informed consent was obtained from all participants.

Study population

For safety analyses, we included patients who received at least one FCM administration and remained on PD for at least 3 months. For efficacy analyses, we selected those PD patients who received at least one FCM administration and had post-baseline assessments after 6 months. Age, comorbid condition or hospital admission were not reasons for exclusion. To evaluate the correction of absolute or relative iron deficiency, we included those patients that were not previously treated with IV iron and with TSAT levels <20% or ferritin <100 ng/mL.

Study outcomes

The effectiveness of FCM was evaluated by monitoring the mean change in ferritin and TSAT levels from baseline over a 12-month follow-up. Secondary outcomes included: the proportion of patients achieving target levels for ferritin and/or TSAT; the proportion of patients using ESAs and the dose received; and accumulated FCM doses throughout the study. To evaluate the ESA dose–response, we calculated an ESA effectiveness index (EEI) by dividing the darbepoetin dose (µg/month) received between visits by the Hb level (g/dL) at the visit. For patients not receiving ESA during an inter-visit period, the EEI was computed as zero. This score is similar to the classic erythropoietin resistance index previously used by other authors to evaluate the individual response to ESAs of a given patient.

To evaluate the safety profile of PD patients after FCM administration, we retrieved safety data from electronic medical

records. Patients spent 1–2 h in the hospital after IV administration during a nurse clinical visit and were instructed to inform in case of any adverse reaction. The incidence of deaths, peritonitis and non-serious AEs (SAEs) was reported when available. SAEs were hypersensitivity reactions or any AE leading to iron withdrawal, hospitalization or emergency department admission.

Iron deficiency and therapy targets were defined based on current NICE, KDIGO and European Renal Best Practices (ERBP) guidelines [4, 8, 30]. Absolute iron deficiency was considered when ferritin levels were <100 ng/mL or TSAT was <20%. The following therapy targets were defined: ferritin between 800 and 200 ng/mL and TSAT >20%. Following the NICE guideline, we considered that FCM doses concurrent with ferritin >800 ng/mL were not recommended [8].

Study treatment

FCM was administered according to the KDIGO guideline and routine clinical practice [4]. Patients who initiated treatment with FCM on PD can be classified into three groups: FCM as first-line treatment, previous unsuccessful oral iron therapy (e.g. poorly tolerated) or switch from HD to PD in those patients who had previously received IV saccharate iron.

Patients were administered a load starting IV infusion of FCM over 20 min at either 500 or 1000 mg in our PD units. Laboratory tests were performed following FCM administration to monitor patients' status without the need for additional visits. Subsequent FCM administrations depended on laboratory results.

Statistical analyses

Continuous variables were described by mean, SD, median and interquartile range, whereas categorical variables were described by number and percentage.

To evaluate changes in continuous variables between visits, we used repeated measures analysis of variance (ANOVA) test with Bonferroni *post hoc* analysis. The level of statistical significance was set at $P < 0.05$. All analyses were performed using the Stata statistical software for Windows, Version 14 (StataCorp LP, College Station, TX, USA).

RESULTS

Study population

Ninety-one patients were included in the safety population and received a total of 229 FCM administrations (26 at 1000 mg and 203 at 500 mg). Mean ± SD age in the safety population was 57.7 ± 15.0 years and 61.9% were male. Of them, 21 were excluded from the efficacy population because they did not have assessments at Month 6 or at subsequent visits (3 were transferred to HD and 18 remained on PD when the study was closed). Therefore, the efficacy population comprised 70 patients (mean ± SD age was 50.9 ± 14.5 years and 68.5% were males). Finally, 51 participants had post-baseline assessments after 12 months (Figure 1). For the efficacy analysis in the correction of absolute or relative iron deficiency, we analysed data from those 51 patients not previously treated with IV iron and with TSAT <20% or ferritin <100 ng/mL.

At baseline, 25% of patients were previously on HD, 10.7% had a previous graft failure and 64.3% were transferred from pre-dialysis outpatient clinics. Participants spent a median of 6 months on PD before the initiation of FCM treatment. Thirty-
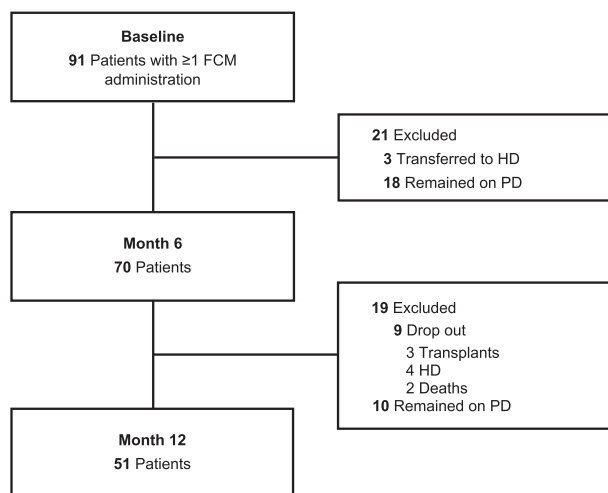

FIGURE 1: Flowchart showing the study design.

Table 1. Demographic and clinical characteristics of patients at baseline

n	91
Age, mean ± SD, years	57.7 ± 15.0
Gender (male), *n* (%)	56 (61.9)
Hb, mean ± SD, g/dL	10.7 ± 1.2
Ferritin, mean ± SD, ng/mL	213.4 ± 145.8
TSAT, mean ± SD, (%)	18.6 ± 7.8
ESA use	
Darbepoetin, *n* (%)	64 (70)
Darbepoetin dose, median (range), µg/month	80 (40.0–160.0)
FCM administrations, *n*	229
1000 mg, *n* (%)	26 (11.4)
500 mg, *n* (%)	203 (88.6)
Aetiology of CKD (%)	
Diabetic nephropathy	23.1
Glomerulonephritis	21.9
Vascular/hypertensive diseases	18.7
Interstitial nephritis	11.0
Polycystic kidney disease	5.5
Other/unknown origin	6.6/13.2

n, number.

one percent of the patients received a previous unsuccessful oral iron trial, 15% other IV iron formulation in a previous HD treatment and the remaining (54%) started with FCM.

Baseline demographic and clinical data are summarized in Table 1.

Safety results

No hypersensitivity reaction, FCM discontinuation or dose adjustment due to an SAE was registered in the patient charts. Among the SAEs, two deaths and seven peritonitis episodes were reported after FCM treatment, but none was considered related to the treatment. We have not registered any discontinuation of FCM treatment during the follow-up.

Eight (8.8%) patients reached mean ferritin levels >800 ng/mL during the follow-up, and only three (3.3%) received FCM administration while ferritin levels were above this upper limit. We identified a feasible cause in most cases (two blood transfusions due to bleeding, one cardiac surgery, two inflammatory conditions such as infection and one malnutrition–

Table 2. Evolution of clinical variables over 12 months of follow-up

Clinical variables	Month 0 (n = 70)	Month 4 (n = 70)	Month 6 (n = 70)	Month 12 (n = 51)
Hb, mean ± SD, g/dL	10.7 ± 1.2	11.9 ± 1.4	11.7 ± 1.3	11.4 ± 1.4
		P < 0.001	P < 0.001	P = 0.03
Ferritin, mean ± SD, ng/mL	213.4 ± 145.8	379.3 ± 267.7	424.7 ± 254.9	452.2 ± 259.6
		P < 0.001	P < 0.001	P < 0.001
TSAT, mean ± SD, %	18.6 ± 7.8	30.4 ± 15.2	30.0 ± 13.0	27.6 ± 11.1
		P < 0.001	P < 0.001	P < 0.001
Darbepoetin use, %	70	80	74.3	48.9*
Darbepoetin dose, μg/month				
Median (IQR)	80 (40–160)	60 (40–120)	60 (40–120)	60 (40–120)
Mean ± SD	76.5 ± 83	71.3 ± 73	65.5 ± 80	55.7 ± 81
EEI, median (IQR), μg/month per g/dL	4.3 (0–12.1)	4.5 (1.7–4.5)	3.4 (0–7.3)	1.4 (0–6.1)*
Accumulated FCM dose, mg	0	1100	1200	1700
Ferritin 200–800 ng/mL, %	45.7	70*	74.3*	68.6*
TSAT >20%, %	34.3	78.7*	78.7*	78.4*
TSAT >25%, %	14.3	60.1*	58.7*	62.8*
TSAT = 20% and ferritin >200 ng/mL, %	15.7	65.8*	67.2*	62.8*

EEI, microgram/month of darbepoetin per gram/decilitre of Hb. Patients not receiving darbepoetin were computed as 0.
P-values were calculated by repeated measures ANOVA and Bonferroni *post hoc* test versus baseline. *P < 0.01 for chi square versus baseline.
IQR, interquartile range.

inflammation–atherosclerosis syndrome), whereas two cases could not be explained by any apparent cause and were likely related to the treatment.

The most common non-SAEs reported after FCM administration were headache (four events), mild hypotension (three events), hypertension (two events), local tattoo due to extravasation (two events) and flare-up of eczema (one event).

Effectiveness results

Participants improved mean ferritin, TSAT and Hb levels upon FCM treatment with a mean ± SD FCM dose of 1700 ± 1032 mg/year and a median of 1500 mg (1000–2500) (Table 2). Mean ferritin and TSAT levels significantly increased from baseline, and a high proportion of patients reached target levels at the end of follow-up (P < 0.01). The review of data from those patients who never reached TSAT levels >20% (3/71) or failed to maintain them after 1 year (11/71) showed the occurrence of comorbid conditions such as cancer (one patient) or intercurrent events such as active bleeding (seven episodes), peritonitis (eight episodes) or other infections (six episodes). Hb levels increased from baseline and were maintained at >11 g/dL during the follow-up with a lower dose of darbepoetin (median doses: 80 μg/month at baseline and 60 μg/month after 12 months). This resulted in a reduction in EEI from 4.3 to 1.4 μg/month/g/dL. The evolution of clinical variables is shown in Table 2.

Dialysis adjustments were performed to maintain adequacy targets. We observed Kt/V stable levels at baseline, 6 and 12 months (Kt/V: 2.3 ± 0.5 versus 2.1 ± 0.5 versus 2.2 ± 0.9) and a decrease in residual renal function (RRF) (RRF: 6 ± 4.7 versus 5.5 ± 4.1 versus 3.5 ± 4.0 mL/min). The mean peritonitis rate was 0.4 episodes per year at risk, and 80% of patients did not present any peritoneal infection during the follow-up. None of the peritonitis cases was diagnosed during the week following FCM administration and were therefore not considered related to the treatment. We found no correlation between these variables and Hb levels.

We observed that iron indices improved across the visits in those 51 patients naïve for IV iron and with iron deficiency. As shown in Table 3, mean ferritin and TSAT levels statistically increased from baseline to Month 4 (increase of 161.5 ng/mL and

12.7%, respectively), resulting in >70% of patients reaching target levels (P < 0.01). Mean accumulated FCM dose was 910 mg during the first 4 months of treatment. An increase in mean Hb levels was observed (from 10.5 to 11.7 g/dL) together with a reduction in EEI from 5.4 to 4.1 μg/month/g/dL.

DISCUSSION

To the best of our knowledge, this is the first observational study assessing the effectiveness and safety of FCM in PD patients by using a therapy regimen adapted to home dialysis.

In this PD population, we evidenced the effectiveness of FCM at improving iron indices and the reduction of ESAs doses without SAEs. One of the major findings of this study is the high proportion of patients achieving clinical targets after FCM initiation. Approximately three-quarters of patients reached the primary endpoint after 6 months and maintained target levels until the end of the 12-month follow-up. Notably, we could identify a clinical cause (comorbid conditions or intercurrent events) in those who did not reach target levels during the follow-up. The reduction of darbepoetin use and doses enabled by the Hb improvement demonstrates the effectiveness of FCM and agrees with previously reported data for HD patients [31].

Current anaemia guidelines recommend IV iron as adjunctive therapy for iron deficiency to treat CKD-related anaemia, but the thresholds of iron targets for the correction of iron deficiency *per se* are far from consensus. Whereas the ERBP proposed to initiate IV iron if TSAT levels are <20% [32], the KDIGO guideline recommends the use of IV iron if an increase in Hb or a decrease in ESA doses are desired and iron status falls below the upper limit (ferritin <500 ng/mL and TSAT <30%) [4]. The rationale for raising the limits was the poor predictive value of TSAT for real iron deficiency and the aim to increase the number of patients that could benefit from iron supplements. The last NICE guideline discourages the use of IV iron if ferritin levels rise above 800 ng/mL [8].

In fact, clinical guidelines do not define a specific target range for iron supplementation but rather a safety limit in different CKD settings. However, information is limited regarding iron targets in the PD population. Thus, in our study, we defined

Table 3. Evolution of clinical variables in patients naïve to IV iron

Clinical Variables	Month 0 (*n* = 51)	Month 2 (*n* = 51)	Month 4 (*n* = 51)
Hb, mean ± SD, g/dL	10.5 ± 1.2	11.6 ± 1.4	11.7 ± 1.3
		$P < 0.001$	$P < 0.001$
Ferritin, mean ± SD, ng/mL	156.3 ± 110.8	342.8 ± 234.9	317.8 ± 175.4
		$P < 0.001$	$P < 0.001$
TSAT, mean ± SD, %	17.1 ± 7.2	27.4 ± 13.4	29.8 ± 14.8
		$P < 0.001$	$P < 0.001$
Darbepoetin dose, mean ± SD, µg/month	89.4 ± 66.8	86.8 ± 67.6	76.5 ± 68.7
Darbepoetin dose, median (IQR), µg/month	80 (40–120)	70 (40–120)	60 (40–80)
EEI, median (IQR), µg/month/g/dL	5.4 (0–10.3)	5.1 (1.8–9.5)	4.1 (1.6–6.8)
Accumulated FCM dose, mg	0	720	910
Ferritin >200 (ng/mL), %	33.3	68.8*	76.5*
TSAT >20%, %	23.5	80.4*	80.4*
TSAT >25%, %	11.1	60.8*	64.7*

EEI, µg/month of darbepoetin per gram/decilitre of Hb. Patients not receiving darbepoetin were computed as 0.
P-values shown were calculated by repeated measures ANOVA and Bonferroni *post hoc* test versus baseline. *P < 0.01 for Chi-square versus baseline.
IQR, interquartile range.

clinical targets (ferritin between 800 and 200 ng/mL and TSAT >20%) by considering these safety recommendations. For example, the UK renal registry showed that the PD population has lower median ferritin levels than the HD population and that less than two-thirds of them fall within the 100–500 ng/mL ferritin range [33].

Only a limited number of studies have addressed the efficacy and safety of IV iron in the PD population [18–26]. Unfortunately, none of them used FCM, sample sizes were small and some of them did not exclusively focus on the PD population [18]. Seven studies, including a total of 147 patients, reported a significant increment in Hb and ferritin levels after a single dose of iron dextran or saccharate [18, 19, 22, 25, 26, 34, 35], and the majority registered a low incidence of AEs upon iron administration. However, most of the studies were conducted during a short-term follow-up for the safety analysis (4 months on average, and only two studies exceeded this follow-up period) [25, 35].

In contrast, evidence of FCM effectiveness is solid in ND-CKD patients as many well-designed studies are available. Qunibi *et al.* [14] showed almost twice the proportion of patients reaching an increase in Hb ≥1.0 g/dL with FCM versus oral iron in a population of 255 subjects [14]. In the FIND-CKD study, FCM enabled higher ferritin and TSAT levels to be reached, maintenance of patients on Hb target and delay and/or reduction of ESA use over a 12-month follow-up [36]. Moreover, a recent meta-analysis comprising data from 2369 patients with CKD Stages 3–5 demonstrated a higher likelihood of achieving a Hb increase >1 g/dL in patients treated with IV versus those treated with oral iron [7].

Current guidelines extrapolate these positive results to the PD population and base their recommendations on both ND-CKD and HD data. In our country, IV iron implementation in PD units is challenged by the lack of scientific evidence in this population, small PD programmes without local experience, complex hospital administration requirements, vein-sparing strategy for future vascular access and safety concerns. In our study, we demonstrated that, under clinical practice conditions, treatment with a high-dose low-frequency strategy with FCM is effective and safe, and eases administration.

The Dialysis outcome and practice patterns study (DOPPS) found an association between higher IV iron doses (≥300 mg/month) and mortality by evaluating data from 32 435 HD

patients (hazard ratio 1.13, 95% confidence interval 1.00–1.27 versus <200 mg/month) [37]. Moreover, it is important to consider the risk of hypersensitive reactions and some evidence about the pro-oxidant effect of IV iron. All these safety concerns led the KDIGO to include the following safety recommendations: to avoid the use of IV iron when ferritin is >800 ng/mL and TSAT is >40%, during active infections and in facilities without trained staff to manage hypersensitivity reactions.

However, we are aware that the risks could differ between PD and HD patients. In this context, the Japanese dialysis report including 191 902 patients receiving dialysis found an association between high ferritin levels and mortality in HD patients but not in PD patients [38]. We previously evidenced that PD patients are younger, less comorbid and with lower iron requirements than HD patients [29].

The PIVOTAL study compared a proactive versus a reactive strategy with IV iron sucrose on 2300 HD patients and reported a lower risk for a composite of events in the high-dose IV iron group, with better control of anaemia and iron, and a similar safety profile [17]. In our study, patients received a median total dose of 1500 mg after 12 months, which is remarkably lower than that in the proactive group of PIVOTAL (median 3200 mg/year for 2 years). However, because of the different study design and study population, our results cannot be directly compared with those of PIVOTAL.

Regarding safety analyses, our main concern was to properly identify anaphylaxis, a reaction than could be over-reported by a deficient differential diagnosis. In our study, we found no single case of hypersensitivity or anaphylactic reaction, not even uncertain descriptions requiring therapy. These results are consistent with those of the FIRM study, showing an incidence of 0.6 and 0.7% of moderate to severe hypersensitivity reactions in patients receiving ferumoxytol and FCM, respectively [39]. Similarly, the high-dose iron formulation of isomaltose iron had an adverse reaction rate of 0.5% with no confirmed episodes of anaphylaxis [40]. Furthermore, the meta-analysis comprising 13 randomized controlled trials found no increased risk of adverse reactions, infections or mortality with IV iron as compared with the oral route of administration [7].

The main strength of this study is that it is the first in reporting the effectiveness and safety of FCM in PD patients. The study employed a comprehensive and well-designed database, which allowed reliable tracking of SAEs that occurred in the

hospital, emergency units or outpatient clinics. In addition, this study did not have restrictive selection criteria and was not limited by the target-achieving strategy of randomized clinical trials. Moreover, it included a considerable sample size and was conducted over a long-term follow-up (12 months).

However, the study also has limitations mainly associated with its observational design, such as the risk of selection bias or the lack of control group, which could limit the external validity of our results. Its retrospective nature also meant that some analyses were limited by the availability of data and the lack of a common PD protocol between PD units. In addition, we acknowledge that non-SAEs could have been left unregistered.

CONCLUSIONS

FCM IV iron treatment is effective and safe to treat iron deficiency anaemia in the PD population. The experience described here with a high-dose and low-frequency strategy with FCM concurrent with routine hospital visits could be easily adapted to home PD, although prospective studies confirming our results are needed.

AUTHORS' CONTRIBUTIONS

J.P.P. supervised the study, contributed to data collection, conceptualization of the idea, study design and statistical analysis, and drafted the article. B.D.G. contributed to data collection and drafted the paper. All authors contributed to data collection and interpretation, and read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

J.P.P. has been the principal investigator in clinical trials sponsored by AMGEN, Roche, Astellas and GSK in the field of anaemia and has received support from AMGEN, Roche, Astellas, GSK and Vifor to attend congresses. L.M.R. has been co-investigator of clinical trials sponsored by GSK and Vifor. The remaining authors declare no conflict of interest. The results presented in this article have not been published previously in whole or part, except in abstract form.

REFERENCES

1. Fishbane S, Pollack S, Feldman HI *et al*. Iron indices in chronic kidney disease in the National Health and Nutritional Examination Survey 1988-2004. *Clin J Am Soc Nephrol* 2009; 4: 57–61
2. Liu H, Yao Y, Cao Y *et al*. Anemia management trends in patients on peritoneal dialysis in the past 10 years. *Int J Clin Exp Med* 2015; 8: 18050–18057
3. Thorp ML, Johnson ES, Yang X *et al*. Effect of anaemia on mortality, cardiovascular hospitalizations and end-stage renal disease among patients with chronic kidney disease. *Nephrology* 2009; 14: 240–246
4. Kidney Disease: Improving Global Outcomes (KDIGO) Anemia Work Group. KDIGO Clinical Practice Guideline for Anemia in Chronic Kidney Disease. *Kidney Int Suppl* 2012; 2: 279–335
5. Eisenga MF, Nolte IM, Van Der Meer P *et al*. Association of different iron deficiency cutoffs with adverse outcomes in chronic kidney disease. *BMC Nephrol* 2018; 19: 225–233
6. Moniem KA, Bhandari S. Bolus intraperitoneal iron versus intravenous iron in peritoneal dialysis patients: a prospective study. *Transfus Alternat Transfus Med* 2007; 9: 101–107
7. Shepshelovich D, Rozen-Zvi B, Avni T *et al*. Intravenous versus oral iron supplementation for the treatment of anemia in CKD: an updated systematic review and meta-analysis. *Am J Kidney Dis* 2016; 68: 677–690
8. National Clinical Guideline Centre. Anaemia management in chronic kidney disease: update 2015. *NICE guideline 8. National Institute for Health and Care Excellence (NICE)*. Updated 2015. http://www.nice.org.uk/guidance/ng8 (4 June 2019, data last accessed)
9. Cada D, Levien T, Baker D. Ferric carboxymaltose. *Hosp Pharm* 2014; 49: 52–59
10. Bregman DB, Goodnough LT. Experience with intravenous ferric carboxymaltose in patients with iron deficiency anemia. *Ther Adv Hematol* 2014; 5: 48–60
11. Ponikowski P, Voors AA, Anker SD *et al*. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2016; 37: 2129–2200
12. Jankowska EA, Tkaczyszyn M, Suchocki T *et al*. Effects of intravenous iron therapy in iron-deficient patients with systolic heart failure: a meta-analysis of randomized controlled trials. *Eur J Heart Fail* 2016; 18: 786–795
13. Anker SD, Kirwan BA, van Veldhuisen DJ *et al*. Effects of ferric carboxymaltose on hospitalisations and mortality rates in iron-deficient heart failure patients: an individual patient data meta-analysis. *Eur J Heart Fail* 2018; 20: 125–133
14. Qunibi WY, Martinez C, Smith M *et al*. A randomized controlled trial comparing intravenous ferric carboxymaltose

with oral iron for treatment of iron deficiency anaemia of non-dialysis-dependent chronic kidney disease patients. *Nephrol Dial Transplant* 2011; 26: 1599–1607

15. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. *Kidney Int* 2015; 88: 905–914

16. Onken JE, Bregman DB, Harrington RA *et al.* Ferric carboxymaltose in patients with iron-deficiency anemia and impaired renal function: The REPAIR-IDA trial. *Nephrol Dial Transplant* 2014; 29: 833–842

17. Macdougall IC, White C, Anker SD *et al.* Intravenous iron in patients undergoing maintenance hemodialysis. *N Engl J Med* 2019; 380: 447–458

18. Besarab A, Chernyavskaya E, Motylev I *et al.* Roxadustat (FG-4592): correction of anemia in incident dialysis patients. *J Am Soc Nephrol* 2016; 27: 1225–1233

19. Ficheux M, Cuny P, Lecouf A *et al.* [Treatment of iron deficiency by a bolus intravenous iron dextran in peritoneal dialysis]. *Néphrologie Thérapeutique* 2011; 7: 558–561

20. Solak Y, Atalay H, Guney I *et al.* Comparison of adverse-event profiles of intravenous low-molecular-weight iron dextran and iron sucrose in peritoneal dialysis patients. *Ren Fail* 2011; 33: 307–311

21. Singh H, Reed J, Noble S *et al.* Effect of intravenous iron sucrose in peritoneal dialysis patients who receive erythropoiesis-stimulating agents for anemia: a randomized, controlled trial. *Clin J Am Soc Nephrol* 2006; 1: 475–482

22. Li H, Wang SX. Intravenous iron sucrose in peritoneal dialysis patients with renal anemia. *Perit Dial Int* 2008; 28: 149–154

23. Ahsan N. Infusion of total dose iron versus oral iron supplementation in ambulatory peritoneal dialysis patients: a prospective, cross-over trial. *Adv Perit Dial* 2000; 16: 80–84

24. Ahsan N. Intravenous infusion of total dose iron is superior to oral iron in treatment of anemia in peritoneal dialysis patients: a single center comparative study. *J Am Soc Nephrol* 1998; 9: 664–668

25. Johnson DW, Herzig KA, Gissane R *et al.* A prospective crossover trial comparing intermittent intravenous and continuous oral iron supplements in peritoneal dialysis patients. *Nephrol Dial Transplant* 2001; 16: 1879–1884

26. Richardson D, Bartlett C, Jolly H *et al.* Intravenous iron for CAPD populations: proactive or reactive strategies? *Nephrol Dial Transplant* 2001; 16: 115–119

27. Smith CH, Jabbar-Lopez ZK, Yiu ZZ *et al.* British Association of Dermatologists guidelines for biologic therapy for psoriasis 2017. *Br J Dermatol* 2017; 177: 628–636

28. Remón-Rodríguez C, Quirós-Ganga P, Portolés-Pérez J *et al.* [Results of the cooperative study of Spanish peritoneal dialysis registries: analysis of 12 years of follow-up]. *Nefrologia* 2014; 34: 18–33

29. Portolés J, Moreno F, López-Sánchez P *et al.* [Peritoneal dialysis and kidney transplant. A two-way ticket in an integrated renal replacement therapy model]. *Nefrologia* 2011; 31: 441–448

30. Locatelli F, Bárány P, Covic A *et al.* Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: A European Renal Best Practice position statement. *Nephrol Dial Transplant* 2013; 28: 1346–1359

31. López-Gómez JM, Portolés JM, Aljama P. Factors that condition the response to erythropoietin in patients on hemodialysis and their relation to mortality. *Kidney Int* 2008; 74: 75–81

32. Locatelli F, Covic A, Eckardt KU *et al.* Anaemia management in patients with chronic kidney disease: a position statement by the Anaemia Working Group of European Renal Best Practice (ERBP). *Nephrol Dial Transplant* 2008; 24: 348–354

33. Gilg J, Evans R, Rao A *et al.* UK Renal Registry 17th Annual Report: Chapter 7 haemoglobin, ferritin and erythropoietin amongst UK adult dialysis patients in 2013: national and centre-specific analyses. *Nephron* 2015; 129: 143–167

34. Singh AK, Szczech L, Tang KL *et al.* Correction of anemia with epoetin alfa in chronic kidney disease. *N Engl J Med* 2006; 355: 2085–2098

35. Prakash S, Walele A, Dimkovic N *et al.* Experience with a large dose (500 mg) of intravenous iron dextran and iron saccharate in peritoneal dialysis patients. *Perit Dial Int* 2001; 21: 290–295

36. Macdougall IC, Bock AH, Carrera F *et al.* FIND-CKD: a randomized trial of intravenous ferric carboxymaltose versus oral iron in patients with chronic kidney disease and iron deficiency anaemia. *Nephrol Dial Transplant* 2014; 29: 2075–2084

37. Bailie GR, Larkina M, Goodkin DA *et al.* Data from the Dialysis Outcomes and Practice Patterns Study validate an association between high intravenous iron doses and mortality. *Kidney Int* 2015; 87: 162–168

38. Maruyama Y, Yokoyama K, Yokoo T *et al.* The different association between serum ferritin and mortality in hemodialysis and peritoneal dialysis patients using Japanese nationwide dialysis registry. *PLoS One* 2015; 10: e0143430

39. Adkinson NF, Strauss WE, Macdougall IC *et al.* Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: a randomized trial. *Am J Hematol* 2018; 93: 683–690

40. Sivakumar C, Jubb VM, Lamplugh A *et al.* Safety of intravenous iron - cosmofer and monofer therapy in peritoneal dialysis and non-dialysis-dependent chronic kidney disease patients. *Perit Dial Int* 2019; 39: 192–195