Original Article

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Assessment of Ferric Carboxymaltose in Iron Deficiency Anaemia Management in Non Dialysis Dependent Chronic Kidney Disease Patients: A Retrospective Observational Study

Urology Section

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ABSTRACT

Introduction: Iron Deficiency Anaemia (IDA) is prevalent in Non Dialysis Dependent Chronic Kidney Disease (NDD-CKD) patients, necessitating effective treatment strategies. Intravenous Ferric Carboxymaltose (FCM) has emerged as a promising therapy due to its single-dose convenience and potential to improve iron parameters.

Aim: To evaluate the efficacy and safety of FCM in correcting IDA and its impact on haematological and renal parameters among NDD-CKD patients.

Materials and Methods: A retrospective observational study was conducted in adult outpatients with advanced CKD {estimated Glomerular Filtration Rate (eGFR) ≤30 mL/min/1.73 m²} from Nephrology clinics across multiple centres (6 hospitals) in India from June 2023 to October 2023. Patients received two doses of 500 mg i.v. FCM. Data on haemoglobin, serum ferritin, Transferrin Saturation (TSAT), C-Reactive Protein (CRP), and eGFR were collected at baseline and after FCM administration. Treatment doses were determined based on individual patient parameters and aimed to achieve ferritin ≥500 ng/mL and TSAT ≥30%. Adverse Events (AEs) were monitored throughout the study period. The data were compared using paired t-test.

Results: A total of 136 patients (males=77 and females=59) were analysed. Significant improvements were observed in haemoglobin levels (+1.48 g/dL, p<0.001), serum ferritin (+55.54 ng/mL, p<0.001), and TSAT (+7.89%, p<0.001) following FCM treatment. There were no serious AEs reported.

Conclusion: Intravenous FCM 500 mg demonstrated efficacy in correcting IDA and improving iron parameters in NDD-CKD patients, with a favourable safety profile. These findings support the use of FCM as a valuable treatment option for managing IDA in this patient population.

Keywords: Estimated glomerular filtration rate, Haemoglobin, Intravenous iron supplement, Safety, Transferrin saturation

INTRODUCTION

Anaemia is a common complication in patients with CKD. In 2021, 1.92 billion people were affected by anaemia, with CKD being one of the major causes [1]. The severity and prevalence of anaemia, in particular, depend on the degree of kidney impairment. It is caused by multifactorial aetiological mechanisms, such as decreased erythropoietic response in bone marrow, decreased erythropoietin production due to kidney failure, iron deficiency from dietary restrictions, decreased half-life of Red Blood Cells (RBC), elevated hepcidin levels related to chronic inflammation, and hyporesponsiveness to Erythropoiesis-Stimulating Agents (ESAs) [2]. Due to these diverse aetiopathologies, many patients continue to be anaemic despite the currently available therapies. The management of anaemia is essential for reducing morbidity and improving the quality of life for CKD patients [2].

Iron deficiency is a commonly observed complication in both dialysis as well as NDD-CKD patients [3]. The common causes include decreased iron absorption as a part of uraemic syndrome, loss of RBCs and iron due to bleeding tendencies in uraemic syndrome, dialysis-related loss of RBCs and iron, and blood loss due to frequent blood tests [4]. In NDD-CKD, anaemia management is done by using either ESAs or iron supplementation [2]. Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guideline for anaemia in CKD patients recommends either oral or intravenous (i.v.) iron for the treatment of iron deficiency in NDD-CKD patients [5]. However, oral iron therapy can be compromised by Gastrointestinal (GI) side effects in >35% of patients, which can result in poor patient compliance and suboptimal iron absorption [6]. The i.v. iron preparations are administered to reduce the risk of side effects, especially when rapid and convenient iron replacement is required. These preparations are available in different formulations with various dosages and dosing frequencies, demonstrating different safety profiles [7].

FCM is a third-generation, dextran-free i.v. iron designed to overcome the limitations of older-generation i.v. iron preparations. It contains a polynuclear iron-oxyhydroxide core stabilised by a polycarboxymaltose shell [8]. It interacts with the reticuloendothelial system, resulting in reduced release of free iron and allowing controlled iron delivery into target tissues [9]. FCM is a robust and stable iron complex that allows selective and controlled delivery of iron into target tissues without releasing large amounts of free or labile iron into the serum [8]. An optimal preparation for i.v. iron replacement therapy should strike a balance between efficiency and safety. Compounds releasing labile iron may cause toxicity, while large molecules can induce antibody formation, leading to anaphylactic reactions. Hence, it is essential to have an i.v. preparation delivering proper amounts of iron in readily available form with the least possible side effects [8]. The safety and efficacy of FCM in NDD-CKD and CHF patients with IDA have been evaluated in international studies, including randomised controlled trials [9-11]. However, data on safety and efficacy in Indian settings are limited. The present study was conducted to assess the efficacy and safety of FCM in the correction of IDA in NDD-CKD patients in the Indian population in a real-world setting.

MATERIALS AND METHODS

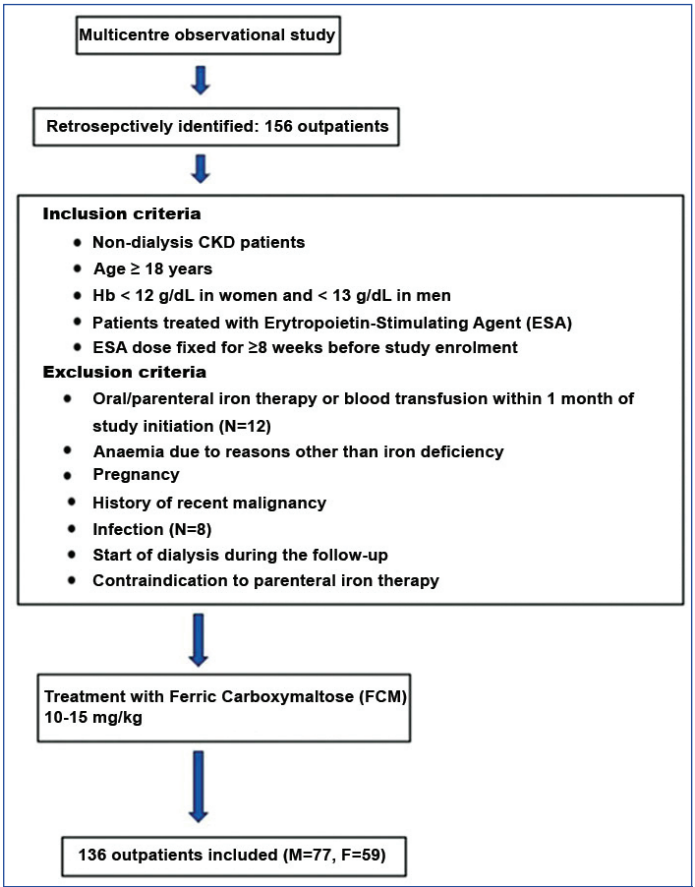
This retrospective, observational AIM NDD CKD, multicentric (6 hospitals in India) study involved adult outpatients with advanced CKD who attended Nephrology clinics in India from June to October 2023. The patient data were analysed in March 2024. The medical records of these patients were reviewed for inclusion criteria, and sociodemographic as well as clinical data were collected via paper Case Report Forms (CRFs). The study protocol was approved by the Independent Ethics Committee of Dhanashree Hospital (Ref No.: IECDH/2023/06).

Inclusion and Exclusion criteria: Inclusion criteria were male and female between 26 and 81 years with NDD-CKD. They must have haemoglobin levels below 12 g/dL for women and below 13 g/dL for men. Participants should be receiving treatment with ESA, with their ESA dose remaining stable for at least eight weeks before enrolling in the treatment. The exclusion criteria included an eGFR <10 mL/min/1.73 m², recent significant GI bleeding or acute blood loss, incomplete medical or follow-up records, early shift to iron therapy, initiation of dialysis, or death during follow-up.

Study Procedure

The study focused on NDD-CKD patients with IDA, who were at least 18 years old and had an eGFR ≤30 mL/min/1.73 m². These patients received two dose of FCM (Encicarb, 500 mg i.v. injection, Emcure Pharmaceuticals Ltd.) and had their iron parameters {Haemoglobin (Hb), serum ferritin, TSAT}, CRP and eGFR measured at baseline and after the second dose of FCM. The diagnosis of IDA was based on the 2012 KDIGO guidelines, requiring Hb concentration below 13.0 g/dL (130 g/L) in males and below 12.0 g/dL (120 g/L) in females, with ferritin ≤500 ng/mL and TSAT ≤30%, along with stable ESA therapy [5].

The study design and patient sample are illustrated in [Table/Fig-1].



[Table/Fig-1]: Flowchart of study design.

The eligible patients received i.v. FCM doses as directed by the physicians, based on the patient's haematological parameters at baseline and guided by prescribing information of FCM. The dose of iron supplementation required was decided with a target-oriented approach aimed at achieving and maintaining ferritin ≥500 ng/mL and TSAT ≥30% [5]. The mean interval between the first and second doses was 14 days. Serious AEs, considering reactions having death, life-threatening situations, or hospitalisation, were recorded; blood pressure during FCM infusion was also reported.

Primary outcome: The primary outcome was the effectiveness of FCM in correcting IDA in NDD-CKD patients, assessed by comparing Hb (g/dL) after last prescribed dose of FCM with the baseline values.

Secondary outcome: The secondary outcome was the change in TSAT (%) and serum ferritin (ng/mL) values at least four weeks after the last administered dose of FCM from the baseline, as well as safety of FCM administration in terms of incidence and severity of AEs recorded after administration of the FCM at each dose. Other parameters, such as CRP (mg/L) as well as eGFR (mL/min/1.73 m²), were also assessed by comparing them to their baseline values.

STATISTICAL ANALYSIS

Descriptive statistics were used to summarise baseline clinical characteristics, with continuous variables presented as means and Standard Deviations (SD) or medians with interquartile ranges (IQR) where appropriate. Categorical variables were expressed as frequencies and percentages. Paired t-tests were used to compare haematological and other clinical parameters before and after FCM administration. The independent variable was FCM administration, and the dependent variables included haemoglobin, serum ferritin, TSAT, CRP and eGFR. All statistical analyses were performed using Microsoft Excel, and a p-value of less than 0.05 was considered statistically significant.

RESULTS

In this retrospective study involving a total of 136 participants, the majority were male (males=77, females=59). Co-morbid disease such as hypertension, were found to be the most common condition in 115 (85%) patients, followed by diabetes in 95 (70%) patients. Cardiac disorders were present in 18 patients. Additionally, 27 patients had received previous oral iron therapy, while 11 had received previous intravenous (i.v.) iron therapy (at least more than a month before baseline data collection) and 31 patients were currently on ESA.

When compared to baseline parameters, a statistically significant increase in mean haemoglobin level was observed post FCM administration (p<0.001) [Table/Fig-2].

Parameters	N	Mean±SD	Median (IQR)	Range	p-value
Haemoglobin (Hb) (g/dL)					
Baseline	136	8.24±1.16	8.40 (7.60-9.00)	4.90-12.40	<0.001
Post FCM (2 dosage)	136	9.72±1.00	9.80 (9.18-10.24)	6.80-12.50	
Serum ferritin (ng/mL)					
Baseline	119	105.30±59.16	96 (78.50-113.5)	2.10-286.70	<0.001
Post FCM (2 dosage)	119	160.84±79.99	180 (100-214)	2.0-300	
TSAT (%)					
Baseline	94	20.07±11.27	17 (14-19)	8.1-50	<0.001
Post FCM (2 dosage)	94	27.96±9.04	27 (21-30)	14-50	

[Table/Fig-2]: Haematological parameters of NDD- CKD patients.
Values are expressed as the mean±standard deviation with significance at p<0.05 (paired t-test)
(CKD: Chronic kidney disease; FCM: Ferric carboxymaltose)

CRP and eGFR data were available at baseline and post FCM for 48 and 23 patient records, respectively. There was a decrease in CRP (mg/L) by a mean of 6.86 (p<0.001) and an increase in eGFR by mean of 0.25 (mL/min/1.73 m²) (p=0.170) post FCM [Table/Fig-3].

Parameters	N	Mean±SD	Median (IQR)	Range	p-value
CRP (mg/L)					
Baseline	48	14.53±14.92	5.60 (3-24)	2.30-50	<0.001
Post FCM (2 dosage)	48	7.67±6.97	4.05 (3.96-10)	2.90-30.8	
eGFR (mL/min/1.73 m²)					
Baseline	23	27.94±13.11	30 (11.50-40.0)	10-46	0.170
Post FCM (2 dosage)	23	28.19±13.08	30 (11.0-40.0)	10-46	

[Table/Fig-3]: Serum CRP and eGFR in NDD-CKD patients.
Values are expressed as the mean±standard deviation with significance at p<0.05 (paired t-test)

AEs reported included back pain, chills, and hypertension in one patient. No serious AEs were reported in any of the subjects.

DISCUSSION

Anaemia in CKD patients can be treated with ESAs and/or iron preparation. Iron preparations can be administered either orally or intravenously. However, taking oral preparations causes poor medication adherence in patients who were frequently taking multiple medications, and it may also result in GI adverse reactions [9]. FCM is a leading intravenous iron therapy, distinguished by its ability to deliver a full 1000 mg iron replacement dose in just a 15 to 60-minute infusion [6,12]. This capability reduces the need for multiple clinic visits, thereby lessening the overall treatment burden on patients. The novel FCM formulation can be administered in a single-dosing regimen (up to 1000 mg, but no more than 15 mg/kg/week) via intravenous infusion over 6 to 15 minutes [13]. This represents a significant advancement in the management of NDD-CKD patients.

There is currently no consensus on the best i.v. iron replacement regimen for adults with CKD, leading to varying local, state, and international guidelines and practices. The Kidney Disease Outcomes Quality Initiative (KDOQI) recommends intravenous iron for maintaining Hb values between 11 and 12 g/dL, ferritin values between 100 and 800 ng/mL, and TSAT values between 20% and 50% [14].

A cohort study of 59 non-haemodialysis CKD patients with IDA who were either intolerant or non-responsive to oral iron received FCM. Each patient received an initial single dose of 500 mg, followed by additional doses if iron deficiency persisted. Over the 24-week study period, patients received an average of 847±428 mg of FCM. The results demonstrated that IDA improved after four weeks of FCM treatment and remained stable. By week 24, the mean changes from baseline were significant: haemoglobin increased by 1.16 g/dL (95% CI: 0.55-1.77), ferritin increased by 104 ng/mL (95% CI: 40-168), and TSAT-increased by 9.5% (95% CI: 5.8-13.2). These improvements were consistent across different clinical settings (non dialysis CKD, peritoneal dialysis, and kidney transplant patients) and were independent of ESA use. Not only did FCM effectively correct IDA in non-haemodialysis CKD patients, but it also resulted in substantial cost savings from the perspectives of society, healthcare systems, and patients [15].

In the present study, a significant improvement (p<0.001) was recorded in the haemoglobin, ferritin, and TSAT after the treatment with FCM. According to Charytan C et al., in a randomised, multicentre study, adults aged 18 to 85 years with CKD were randomised into an FCM group and Standard Medical Care (SMC) group. In the FCM group, NDD-CKD patients (n=204) received an undiluted i.v. dose of FCM (15 mg/kg, to a maximum of 1000 mg). In the SMC group, NDD-CKD patients (n=212) received either oral iron, i.v. iron, or no iron. FCM, in doses up to 1000 mg in NDD-CKD patients, was well tolerated and displayed comparable efficacy to other i.v. iron formulations [14].

Although FCM dosing was dependent on baseline haemoglobin and weight of patient, in this real-world observational study, dosing of FCM was as per the physician's discretion. The present study showed that an average total dose of 1000 mg in two divided doses of 500 mg during each infusion was the preferred dose for iron replacement in NDD-CKD patients. Additionally, the median patient weight was 69 kg. The dosing method used was 15 mg/kg, leading to a total iron dose calculation of approximately 1000 mg. This explains why the majority of patients received two doses of 500 mg each.

In 56-week randomised, open-label, multicentre FIND-CKD study, NDD-CKD patients received either high ferritin-targeted FCM (400-600 µg/L), low ferritin-targeted FCM (100-200 µg/L), or oral iron. The change in eGFR from baseline to month 12 was +0.7 mL/min/1.73 m² with high ferritin FCM, -0.9 mL/min/1.73 m² with low ferritin FCM, and -0.9 mL/min/1.73 m² with oral iron, with no significant differences between groups. There was no significant association between FCM dose, ferritin change, or TSAT change, and eGFR change. Renal AEs were rare with no significant differences. Thus, i.v. FCM did not negatively impact renal function over 12 months compared to oral iron, showing no evidence of renal toxicity in NDD-CKD patients [10].

A real-life study by Hofman JMG et al., showed that while the weekly iron dosage was considerably lower when haemodialysis patients got FCM compared to Iron Sucrose (48 vs. 55 mg/week, p=0.04), the haemoglobin rose in all groups (anaemic: 1.4 g/dL, p<0.001; iron deficient: 0.6 g/dL, p<0.001). Additionally, all groups (anaemic: 64 µg/L, 5.0%, p<0.001; iron deficient: 76 µg/L, 3.6%, p<0.001) showed increases in serum ferritin and transferrin saturation [16].

CRP (mg/L) (p<0.001) and eGFR (mL/min/1.73 m²) (p=0.170) were found to be significant. The CRP for 60 patients decreased from a mean baseline reading of 14.53±14.92 mg/L to 7.67±6.97 mg/L post FCM administration. While, the eGFR increased from 27.94±13.11 to 28.19±13.0842 mL/min/1.73 m². Deterioration of renal function may also influence the level of other inflammatory molecules, such as serum CRP or IL-6, whose concentration inversely correlates with creatinine clearance. The decrease in CRP may indicate the role of iron therapy in decreasing inflammation [17].

In a study by Ponikowski P et al., the eGFR (mL/min/1.73 m²), derived from the CKD Epidemiology Collaboration (CKD-EPI) formula, was used to evaluate renal function at baseline as well as at weeks 4, 12, and 24. The improvement in eGFR was statistically significant at week 24 and consistent across all pre specified subgroups. There was no interaction between the favourable effects of FCM on eGFR and baseline renal function. The safety and adverse event profiles were similar, regardless of whether patients had baseline eGFR below or above 60 mL/min/1.73 m². In conclusion, FCM treatment in CHF patients with iron deficiency was associated with a significant improvement in eGFR over 24 weeks, demonstrating its efficacy and safety in patients with renal dysfunction. In short, treatment with FCM was linked to an increase in eGFR compared with placebo [11]. None of the patients reported any adverse effects.

In a study by Vikrant S and Parashar A, FCM was found to be safe and efficient at high dose of administration in anaemic CKD patients [9]. FCM in this study was administered as an i.v. infusion of 1000 mg in 250 mL of normal saline over 15-30 minutes. None of the patients reported any serious drug-related adverse events.

Limitation(s)

This study has several limitations. The retrospective design may introduce selection bias and limit the ability to establish causation. The sample size is relatively small, particularly for certain parameters like CRP and eGFR, which were available for only a subset of patients. Also, the lack of a control group limits the ability to compare outcomes against other treatment approaches. The limited sample size and regional focus may constrain the broader applicability of the findings. Future research with larger sample sizes, extended follow-up periods, and comparisons to other intravenous iron dosages is necessary to validate these findings and investigate long-term outcomes.

CONCLUSION(S)

This study demonstrated the efficacy and safety of FCM in improving haematological parameters. These results from real-world Indian data support that i.v. FCM administered in two doses of 500 mg is a safe and effective treatment for the correction of IDA in NDD-CKD patients.

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