

The Impact of Intravenous Iron on Renal Injury and Function Markers in Patients With Chronic Kidney Disease and Iron Deficiency Without Anemia



Xenophon Kassianides¹, Adil Mohammad Hazara¹, Iain C. Macdougall², Philip A. Kalra³ and Sunil Bhandari¹

¹Academic Renal Research Department, Hull University Teaching Hospitals NHS Trust and Hull York Medical School, Hull, UK; ²Department of Renal Medicine, King's College Hospital, London, UK; and ³Department of Renal Medicine, Salford Royal NHS Foundation Trust and University of Manchester, Manchester, UK

Correspondence: Sunil Bhandari, Academic Renal Research Department, Hull University Teaching Hospitals NHS Trust and the Hull York Medical School, Kingston Upon Hull, HU32JZ, UK. E-mail: sunil.bhandari@nhs.net

Received 18 September 2021; revised 25 October 2021; accepted 1 November 2021; published online 24 November 2021

Kidney Int Rep (2022) 7, 322–326; <https://doi.org/10.1016/j.ekir.2021.11.002>

KEYWORDS: chronic kidney disease; cystatin C; ferric derisomaltose; intravenous iron; iron deficiency; neutrophil gelatinase associated lipocalin

© 2021 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

INTRODUCTION

Intravenous (i.v.) iron is often used in the management of iron deficiency anemia in patients with nondialysis-dependent chronic kidney disease (CKD). Guidelines advocate a “high dose, low frequency approach,” which is more easily achievable in modern practice owing to new i.v. iron therapies.¹ Concerns however persist regarding hypersensitivity and oxidative stress.¹ These arise owing to earlier experience with older i.v. iron compounds (e.g., iron sucrose) suggesting possible nephrotoxicity owing to increased proteinuria, a phenomenon credited both directly and indirectly to oxidative damage.²

Newer (third generation) i.v. iron preparations (ferric carboxymaltose, ferric derisomaltose [FDI], ferumoxytol) have a more compact structure and exhibit different modes of iron release compared with their predecessors.³ This limits their pro-oxidant effect and potentially any resulting nephrotoxicity. As there is increasing real-world evidence on the utility and cost-effectiveness of high-dose treatment with third-generation i.v. iron preparations in populations with non-dialysis-dependent CKD,⁵¹ it is important to explore whether any negative renal impact exists after their administration.

As part of the multicenter, double-blind, pilot, randomized, controlled “Iron & Heart” trial, markers of renal function (cystatin C and creatinine) and injury (proteinuria—glomerular damage, neutrophil-associated lipocalin

[NGAL]—tubular damage) were measured. The study was primarily designed to evaluate the impact of i.v. iron (FDI) at a high dose (1000 mg) in patients with non-dialysis-dependent CKD and iron deficiency but not anemia on 6-minute walk test, as an objective measure of functional status.⁴ This was performed to establish whether similar positive effects as those exhibited in patients with heart failure exist in this population. Here, we report on the renal-associated secondary objectives evaluating the renal effect of high-dose FDI in this patient group ([Supplementary Methods](#)).

RESULTS

A total of 54 patients were recruited and randomized to receive FDI ($n = 26$) or placebo ($n = 28$). Baseline characteristics of the study participants are presented in [Table 1](#). The 2 groups were well-matched with no significant differences in the majority of characteristics. Although baseline serum creatinine was significantly lower in the FDI group (158 vs. 201 $\mu\text{mol/L}$, $P = 0.03$), estimated glomerular filtration rate (eGFR) calculated using both creatinine and cystatin C were not significantly different between the 2 groups.

After the FDI infusion, no significant changes were detected in the serum levels of creatinine and cystatin C nor the eGFR ([Supplementary Figures S1 and S2](#)). At baseline, the eGFR of participants in the FDI group was greater than those receiving placebo; this overall advantage was not altered throughout the study. There were no

Table 1. Baseline characteristics

Characteristic	FDI	Placebo	P value
N	26	28	
Age, median	61	59	0.34
Sex, male	11 (44%)	15 (54%)	0.49
Ethnicity			
White	19 (73%)	23 (82%)	0.59
Black	4 (15%)	3 (11%)	
Other	3 (12%)	2 (7%)	
Smoking			
No	17 (65%)	15 (54%)	0.38
Yes—current	1 (4%)	4 (14%)	
Yes—former	8 (31%)	9 (32%)	
BMI, mean (SD)	30.768 (6.878)	30.01 (6.438)	0.71
Primary renal disease			
Diabetes	8 (31%)	9 (32%)	0.99
Hypertension	2 (8%)	2 (7%)	
Glomerulonephritis	7 (27%)	6 (21%)	
Adult polycystic kidney disease	2 (8%)	3 (11%)	
Reflux nephropathy	1 (4%)	2 (7%)	
Other/unknown	6 (23%)	6 (21%)	
Blood pressure, mean (SD)			
Systolic, mm Hg	138.2 (19.9)	129.4 (18.45)	0.098
Diastolic, mm Hg	78.5 (10.7)	76.2 (11.8)	0.45
Laboratory measures, median			
Creatinine, $\mu\text{mol/L}$	158 (134, 181)	201 (161, 254)	0.032 ^a
eGFR-creat, ml/min per 1.73 m ²	35 (26, 43)	26 (22, 36)	0.12
Cy C, mg/L	2.13 (1.72, 2.53)	2.28 (1.90, 2.76)	0.24
eGFR-Cy, ml/min per 1.73 m ²	28 (21, 36)	26 (20, 31)	0.27
Hemoglobin, g/L mean (SD)	131.0 (7.4)	126.5 (11.8)	0.10
Ferritin, $\mu\text{g/L}$	55.0 (45.0, 79.0)	50.0 (26.0, 82.0)	0.37
Transferrin saturations, %	19.5 (16.0, 27.0)	19.0 (15.0, 21.0)	0.43
C-reactive protein, mg/L	4.0 (2.4, 9.5)	4.0 (2.2, 4.3)	0.32
Urinary albumin:creatinine, mg/mmol	5.9 (2.1, 48.4)	19.5 (3.3, 90.7)	0.33
NGAL, ng/ml	323.51 (252.94, 409.08)	365.29 (305.15, 430.16)	0.17

BMI, body mass index; creat, creatinine; Cy, cystatin; eGFR, estimated glomerular filtration rate; FDI, ferric derisomaltose; NGAL, neutrophil-associated lipocalin.

^a $P < 0.05$

significant changes in the serum levels of NGAL in either of the treatment arms throughout the follow-up period. In the FDI group, NGAL levels at baseline, 1 month, and 3 months were 323.5, 313.9, and 356.1 ng/ml, respectively (baseline–1 month: $P = 0.39$; baseline–3 months: $P = 0.29$) and 365.2, 370.7, and 390.6 ng/ml, respectively, in the placebo group (baseline–1 month: $P = 0.73$; baseline–3 months: $P = 0.71$) (Figure 1).

Urinary albumin-creatinine ratio measurements were available for 22 participants in the FDI group and 24 in the placebo group. Urinary albumin-creatinine ratio levels did not change significantly post infusion in either treatment arm (Figure 2). In the FDI group, urinary albumin-creatinine ratio levels at baseline, 1 month, and 3 months were 5.9, 6.2, and 7.1 mg/mmol, respectively (baseline–1 month: $P = 0.44$; baseline–3 months: $P = 0.28$), and 19.5, 19.3, and 26.7 mg/mmol, respectively, in the placebo group (baseline–1 month: $P = 1.00$; baseline–3 months: $P = 0.75$).

DISCUSSION

In this study, kidney injury and function markers remained unchanged after administration of high-dose FDI at 1 and 3 months. FDI use was not associated with increases in serum levels of NGAL, a sensitive marker of acute renal tubular damage, or increases in proteinuria throughout follow-up. These findings suggest that FDI did not lead to any short term tubular or glomerular injury.

A proteinuric effect of i.v. iron has been previously displayed in patients receiving iron sucrose (100 mg) when compared with oral iron, within 15 minutes of administration.² Despite a return to baseline within 24 hours, that study concluded that certain i.v. iron compounds could be associated with nephrotoxicity. In this study, with FDI, there was no increase in proteinuria level at any follow-up point compared with placebo. In addition, there was no statistically significant change in NGAL with FDI treatment, similar to the IRON-TURTLE trial using a dose of 1000 mg of ferric

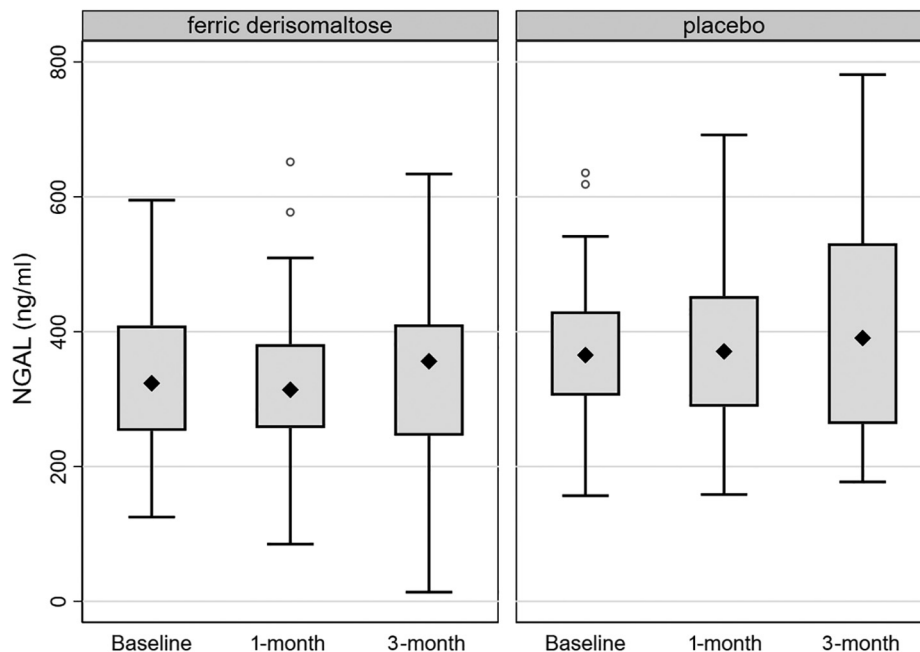


Figure 1. Changes in serum levels of NGAL during the follow-up period in the 2 treatment groups. *P* values nonsignificant for all pairwise comparisons between baseline versus 1-month and baseline versus 3-month values. NGAL, neutrophil-associated lipocalin.

carboxymaltose in patients with heart failure and CKD and correlating with *in vivo* and *in vitro* evidence relevant to third-generation i.v. iron compounds.^{5,6} Indeed, such evidence has indicated that third-generation i.v. iron compounds seem to be “bio-neutral” in terms of renal injury and oxidative stress when compared with earlier preparations.^{5,2}

In this study, no detriment in terms of creatinine or cystatin C (and their derived eGFR) was observed with FDI compared with placebo. This is in agreement with

previous studies with non-dialysis CKD participants.^{5,7,8} The REVOKE trial ($n = 136$, non-dialysis-dependent CKD with iron deficiency anemia) compared i.v. iron sucrose with oral iron in terms of measured glomerular filtration rate using iothalamate clearance in a 2-year period.⁷ Measured glomerular filtration rate declined similarly irrespective of treatment modality and after additional demographic, medication, and comorbidity adjustments.⁷ During the FIND-CKD trial, 626 non-dialysis-dependent CKD patients were

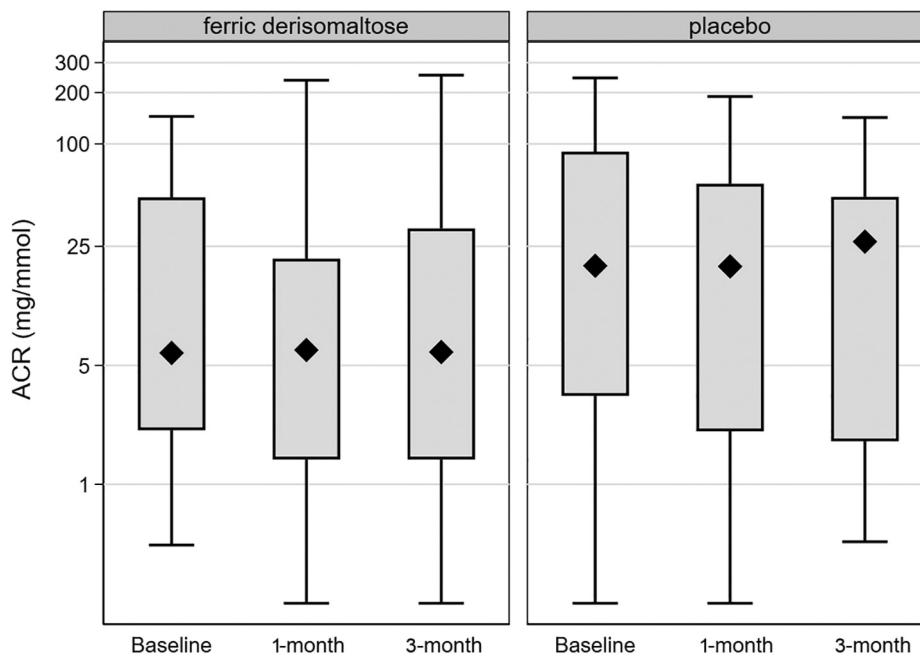


Figure 2. Changes in urinary albumin-to-creatinine ratio during the follow-up period in the 2 treatment groups. *P* values nonsignificant for all pairwise comparisons between baseline versus 1-month and baseline versus 3-month values. Note that the ACR results are found on a logarithmic scale. ACR, albumin-creatinine ratio.

randomized to oral iron or i.v. ferric carboxymaltose and similarly demonstrated no difference in eGFR between the 2 treatment modalities in a 12-month period.⁸ In patients with CKD and reduced ejection fraction, administration of high dose ferric carboxymaltose also did not produce any impact on cystatin C or other markers of renal function.⁵ It is noteworthy that an analysis of the FAIR-HF trial evaluating the impact of ferric carboxymaltose in patients with established systolic heart failure concluded that correction of iron deficiency with i.v. ferric carboxymaltose led to a statistically significant improvement in eGFR when compared with placebo.⁹

The neutral results of this study on renal injury may be caused by a combination of factors potentially associated with the iron preparation used. Intriguingly, alleviation of iron deficiency may be renoprotective with recent evidence suggesting correction of iron deficiency in murine uremic models promotes an overall antioxidant effect, whereas the notion of renal preconditioning through activation of the NRFT2 pathway is also explored.^{S3,S4}

Several limitations are present in this study, and the results therefore need to be treated with caution. The study did not focus on an ultra-acute effect of i.v. iron as that previously displayed in literature. This study focused on short- to medium-term renal damage after i.v. iron administration, and it is therefore not possible to draw any conclusions on a potential cumulative effect of repeated iron administrations. In addition, as these are secondary outcomes, the study is underpowered to detect true statistical significance.

In conclusion, the results from the Iron and Heart trial with FDI treatment add further to the safety evidence surrounding the use of i.v. iron in patients with non-dialysis-dependent CKD, especially in terms of renal injury and function. Further markers of nephrotoxicity can be incorporated in such research (e.g., urinary NGAL, beta-2-microglobulin) to investigate further possible renal injury. These results are reassuring with regard to the safety of conducting further large-scale trials in the treatment of iron-deficient patients with CKD but not anemia to identify any impact on quality of life and functional status, similar to that already found in patients with heart failure.

DISCLOSURE

SB, ICM, and PAK have received honoraria for lectures, attended expert opinion committees and advisory boards, and received educational funds to attend international nephrology meetings from Pharmacosmos A/S and Vifor Pharma. XK and AMH declared no competing interests.

ACKNOWLEDGMENTS

This study received a favorable opinion from the Northern Regional Ethics Service (NRES) Committee Yorkshire & The Humber-Leeds East, United Kingdom (approval reference number 10/H1306/40) and has been registered with the European Union Drug Regulating Authorities Clinical Trials Database (EudraCT number: 2014-004133-16). The authors thank all participants in the study for their kind cooperation throughout and the teams facilitating iron delivery and maintenance of the database in London (King's College Hospital), Hull (Hull Royal Infirmary), and Manchester (Salford Royal Infirmary) (including Vikki Jubb, Archie Lamplugh, and Ahmed Ziedan). The Iron & Heart study received funding from the Kidney Research UK by an unrestricted grant from Pharmacosmos A/S to support all aspects of the study. The funders had no role in the study design, data collection and analysis, and preparation of the manuscript for publication.

AUTHOR CONTRIBUTIONS

XK was involved in the collection, maintenance, analysis and interpretation of data and drafting the article. AMH was involved in the analysis and interpretation of data and critical revision of the article. SB (chief investigator) participated in all aspects of the study, obtained funding for the study, and critically revised the manuscript. ICM and PAK contributed to the design of the study and critically reviewed the drafts of the manuscript. All authors have provided intellectual content of critical importance to the work described and have read and approved the final version to be published. The order of authorship has been a joint decision of the co-authors based on substantial contribution to conception and design, execution, analysis, and interpretation of data.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Figure S1. Changes in serum creatinine and cystatin C in the FDI and placebo groups.

Figure S2. Changes in eGFR in the FDI and placebo groups.

REFERENCES

1. Kassianides X, Hazara AM, Bhandari S. Improving the safety of intravenous iron treatments for patients with chronic kidney disease. *Expert Opin Drug Saf.* 2021;20:23–35. <https://doi.org/10.1080/14740338.2021.1853098>
2. Agarwal R, Rizkala AR, Kaskas MO, et al. Iron sucrose causes greater proteinuria than ferric gluconate in non-dialysis chronic kidney disease. *Kidney Int.* 2007;72:638–642. <https://doi.org/10.1038/sj.ki.5002422>
3. Kassianides X, Bodington R, Bhandari S. An evaluation of ferric derisomaltose as a treatment for anemia. *Expert Rev Hematol.* 2021;14:7–29. <https://doi.org/10.1080/17474086.2021.1858406>

4. Bhandari S, Allgar V, Lamplugh A, Macdougall I, Kalra PA. A multicentre prospective double blinded randomised controlled trial of intravenous iron (ferric derisomaltose (FDI)) in iron deficient but not anaemic patients with chronic kidney disease on functional status. *BMC Nephrol.* 2021;22:115. <https://doi.org/10.1186/s12882-021-02308-y>
5. Brandenburg V, Heine GH, Marx N, Stöhr R. Sharp rises in FGF23 and hypophosphatemia after intravenous iron administration do not cause myocardial damage. *Clin Res Cardiol.* 2020;109:1316–1318. <https://doi.org/10.1007/s00392-020-01630-z>
6. Johnson ACM, Becker K, Zager RA. Parenteral iron formulations differentially affect MCP-1, HO-1, and NGAL gene expression and renal responses to injury. *Am J Physiol Ren Physiol.* 2010;299:F426–F435. <https://doi.org/10.1152/ajprenal.00248.2010>
7. Agarwal R, Kusek JW, Pappas MK. A randomized trial of intravenous and oral iron in chronic kidney disease. *Kidney Int.* 2015;88:905–914. <https://doi.org/10.1038/ki.2015.163>
8. 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. <https://doi.org/10.1093/ndt/gfu201>
9. Ponikowski P, Filippatos G, Colet JC, et al. The impact of intravenous ferric carboxymaltose on renal function: an analysis of the FAIR-HF study. *Eur J Heart Fail.* 2015;17:329–339. <https://doi.org/10.1002/ejhf.229>