Ferric Derisomaltose Evaluation in Patients with Non–Dialysis-Dependent Chronic Kidney Disease or Peritoneal Dialysis

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ABSTRACT

Background: Iron deficiency anemia is common in patients with advanced chronic kidney disease (CKD). Ferric derisomaltose (FDI) enables iron repletion in a single dose, unlike other forms of iron for IV administration, which require multiple doses. Protocols are commonly used with other IV irons, but there are limited Canadian data for FDI, and no protocol exists.

Objectives: To evaluate the efficacy and safety of FDI for patients with CKD and to ascertain information related to its use in Canadian provinces.

Methods: This retrospective cohort study involved patients with non–dialysis-dependent CKD (NDD-CKD) and patients undergoing peritoneal dialysis (PD) who received FDI in a tertiary hospital in Nova Scotia between June 2020 and May 2021. Each patient was followed for a minimum of 6 months. The efficacy outcomes were the changes from baseline in hemoglobin, transferrin saturation (TSAT), and ferritin after the first dose of FDI and at 3 and 6 months. The safety outcomes were the frequency and types of adverse reactions to FDI. Electronic surveys were sent to 33 Canadian renal pharmacists to gather information about FDI use, dosing, administration, monitoring, funding, and safety in their respective organizations.

Results: A total of 52 infusions were administered to 35 patients during the study period. The median times between doses 1 and 2 and between doses 2 and 3 were 19.1 and 6.6 weeks, respectively. The median change from baseline to first post-FDI follow-up blood work was significant for hemoglobin (9.0 g/L, $p = 0.023$), TSAT (11 percentage points, $p < 0.001$), and ferritin (271.4 µg/L, $p < 0.001$). Median darbepoetin doses decreased from baseline to 6 months ($p < 0.001$). Three adverse reactions occurred. At least 15 (65%) of the 23 survey respondents reported that FDI was funded by their province or was listed on their hospital drug formulary.

Conclusion: This study provides evidence that FDI is an effective and safe treatment for anemia in NDD-CKD and PD patients.

Keywords: ferric derisomaltose, iron isomaltoside, IV iron, anemia, chronic kidney disease, peritoneal dialysis

RÉSUMÉ

Contexte : L'anémie ferriprive est fréquente chez les patients atteints d'insuffisance rénale chronique avancée (IRC). Une seule dose de dérisomaltose ferrique (FDI) permet au niveau de fer de se rétablir, contrairement à d'autres formes de fer administrées par IV qui nécessitent, elles, plusieurs doses. Des protocoles sont couramment utilisés avec d'autres fers administrés par IV, mais les données canadiennes sur le FDI sont limitées et il n'existe aucun protocole.

Objectifs : Évaluer l'efficacité et l'innocuité du FDI chez les patients atteints d'IRC et vérifier les informations relatives à son utilisation dans les provinces du Canada.

Méthodes : Cette étude de cohorte rétrospective comprenait des patients atteints d'IRC sans dialyse (NDD-IRC) et des patients sous dialyse péritonéale (DP) ayant reçu du FDI dans un hôpital de soins tertiaires de la Nouvelle-Écosse entre juin 2020 et mai 2021. Chaque patient a fait l'objet d'un suivi pendant au moins 6 mois. Les résultats d'efficacité étaient les changements par rapport à la base de trois mesures après la première dose de FDI et à 3 et 6 mois, soit l'hémoglobine, la saturation de la transferrine (TSAT) et la ferritine. Les résultats d'innocuité étaient la fréquence et les types de réactions indésirables au FDI. Des sondages ont été envoyés par voie électronique à 33 pharmaciens canadiens spécialisés en néphrologie afin de recueillir des renseignements sur l'utilisation, le dosage, l'administration, la surveillance, le financement et l'innocuité du FDI dans leurs organismes respectifs.

Résultats : Au total, 52 perfusions ont été administrées à 35 patients au cours de la période d'étude. Les délais médians entre les doses 1 et 2, et entre les doses 2 et 3 étaient respectivement de 19,1 et 6,6 semaines. Le changement médian entre la base et le premier bilan sanguin de suivi post-FDI était important pour l'hémoglobine (9,0 g/L, $p = 0,023$), le TSAT (11 points de pourcentage, $p < 0,001$) et la ferritine (271,4 µg/L, $p < 0,001$). Les doses médianes de darbépoétine ont diminué par rapport à la base à 6 mois ($p < 0,001$). Trois effets indésirables se sont produits. Au moins 15 des 23 répondants au sondage (65 %) ont déclaré que le FDI était financé par leur province ou figurait sur les listes de médicaments des hôpitaux.

Conclusion : Cette étude fournit des preuves que le FDI est un traitement efficace et sûr de l'anémie chez les patients NDD-IRC et PD.

Mots-clés : dérisomaltose ferrique, isomaltoside de fer, fer IV, anémie, maladie rénale chronique, dialyse péritonéale

INTRODUCTION

Iron deficiency anemia is a common complication associated with chronic kidney disease (CKD), and its prevalence increases with advancing stages of CKD.[1,2] Factors associated with iron deficiency in CKD include reduced gastrointestinal absorption of iron, blood loss, use of erythropoiesis-stimulating agents (ESAs), which increase the demand for iron, and inefficient utilization of iron stores due to chronic inflammation and increased hepcidin levels.[3] Iron deficiency, combined with inadequate production of erythropoietin by the kidneys, results in decreased erythropoiesis leading to anemia. Untreated anemia in patients with CKD has been associated with reduced quality of life, progression of kidney disease, and adverse clinical and economic outcomes.[4,5]

Iron supplementation is an established therapy to treat iron deficiency and enhance the efficacy of ESAs in those with CKD.[6-8] International and Canadian anemia guidelines advocate for the use of iron by adult CKD patients who have anemia, irrespective of their use of ESAs. These guidelines recommend treatment with IV iron or alternatively 1–3 months of oral iron in patients with non–dialysis-dependent chronic kidney disease (NDD-CKD) if an increase in hemoglobin without starting ESA or a decrease in ESA dose is desired.[7]

Although oral iron is more accessible, IV iron may be necessary to treat anemia in patients with NDD-CKD and those receiving peritoneal dialysis (PD), particularly if oral iron is not tolerated or does not yield the desired hematological response. Moreover, oral iron has been reported to be less efficacious than parenteral iron in patients with stage 4 or 5 CKD and in PD patients.[6,9,10]

Ferric derisomaltose (FDI), previously known as iron isomaltoside 1000 (produced by Pharmacosmos A/S, Denmark; imported/distributed by Pfizer Canada ULC, Quebec), is the newest IV iron agent to be marketed in Canada; in this country, it is branded as Monoferric. It is a high-dose formulation that can be administered in a single infusion of up to 20 mg/kg body weight (maximum single dose of 1500 mg).[11] FDI is an iron carbohydrate complex with a matrix structure composed of alternating layers of ferric hydroxide and the carbohydrate derisomaltose.[11] This strongly bound complex enables a slow, controlled release of bioavailable iron to iron-binding proteins with minimal risk of toxic effects from labile iron. This allows for single-dose iron repletion in patients with CKD, whereas traditional IV iron preparations require between 3 and 10 doses for repletion. More rapid iron repletion has benefits for both patients and hospitals, such as quicker improvements in anemia-related symptoms, avoidance or minimization of more expensive ESA therapy or blood transfusions, preservation of venous access, reduced chair time resulting in less time lost from work, and greater capacity for hospitals to administer IV iron.

Data from clinical and observational trials outside Canada have reported good efficacy and safety of FDI in CKD patients with anemia.[12-22] Given Health Canada safety warnings and subsequent market withdrawal of the first large-dose IV iron preparation, ferumoxytol, in 2014,[23] clinicians have been cautious in prescribing FDI, and real-world experience with this formulation is therefore limited.

Standardized anemia protocols for ESA and traditional IV iron therapies are frequently used in Canada for maintenance anemia management in patients with CKD.[24-27] However, there is currently no FDI protocol available to aid clinicians in the maintenance management of iron deficiency anemia in CKD patients. We evaluated the real-world efficacy and safety of FDI in NDD-CKD and PD patients and endeavoured to better understand its use in Canada through a survey of renal pharmacists.

METHODS

Efficacy and Safety Evaluation

This retrospective cohort study involved consecutive NDD-CKD and PD patients who received an initial dose of IV FDI in our hospital's medical day unit from June 1, 2020, to May 31, 2021. The research protocol was approved by, and received a waiver exemption from, the hospital research ethics board, as the study was deemed to be a quality assurance study. Individual patient consent was not required. The study was conducted in accordance with STROBE guidelines.[28]

The Nova Scotia Health Renal Program provides anemia management to approximately 250 NDD-CKD (stage 4 or stage 5) and PD patients within the largest zone of the provincial health authority. Twenty-five percent of these patients require IV iron periodically or for long-term maintenance therapy to treat iron deficiency anemia. Prescriptions for IV iron are based on a hospital order set. Anemia in NDD-CKD and PD patients is comanaged by a nephrologist and a nurse, including routine blood work performed every 4–6 weeks according to standardized protocols, with targets for hemoglobin (Hgb) and iron indices being based on best practice for ESAs, oral iron, and IV iron sucrose.[7] No protocol is available for IV administration of FDI.

For purposes of this study, the medical day unit assistant notified the renal pharmacist (M.S.) when patients were booked for FDI infusion. Eligible patients with the conditions of interest were those who received an initial dose of IV FDI 1000 mg (or 2 doses of 500 mg separated by 1 week) for transferrin saturation (TSAT) less than 20% and/or ferritin less than 100 µg/L during the study period. Each FDI dose was diluted in 100 mL sodium chloride 0.9% and administered as an infusion over 20 minutes, as per the Canadian product monograph.[11] Each patient was followed for a minimum of 6 months and up to 18 months after the initial infusion. Patients were excluded if another form of

IV iron (i.e., iron sucrose, sodium ferric gluconate) was administered during the study period.

Hospital electronic medical records and the provincial drug information system were used to retrieve the following baseline clinical and demographic characteristics: age, sex, weight, estimated glomerular filtration rate, modality (stage 4 or 5 CKD or PD), comorbidities, cumulative monthly dose of darbepoetin alfa and of iron sucrose, daily dose of elemental oral iron, and laboratory parameters (specifically Hgb, TSAT, and ferritin). Electronic medical records were also used to obtain timing and values for Hgb, TSAT, and ferritin after the initial FDI infusion and at 3 and 6 months, as well as the timing of subsequent FDI infusions. Laboratory values within 45 days of the 3- and 6-month evaluation time points after FDI infusion were included. Electronic drug databases were used to collect data for oral iron and darbepoetin alfa doses at the 3- and 6-month assessment time points. Adverse effects related to FDI during and up to 60 minutes after the infusion were collected from nursing progress notes in the electronic medical records and patient incident reports.

The primary efficacy objectives were to evaluate (1) the changes in Hgb, TSAT, and ferritin from baseline to next routine blood work after the FDI infusion and (2) overall effectiveness, as determined by the changes in Hgb, TSAT, and ferritin from baseline to 3 and 6 months after FDI infusion. The primary safety objective was to determine the types and frequencies of adverse reactions to FDI (i.e., anaphylaxis, Fishbane reaction, isolated reaction), as assessed by 2 independent investigators (renal pharmacists J.W. and M.S.) using previously described criteria.[29] The secondary objective was to evaluate, at 3 and 6 months, the change from baseline in concomitant anemia medications (i.e., darbepoetin alfa and oral elemental iron).

Descriptive statistics (mean and standard deviation [SD]) were used for continuous data and percentages for categorical data in reporting patients' demographic, clinical, and laboratory characteristics. Changes in laboratory parameters (i.e., Hgb, TSAT, ferritin) were presented as means with SDs and medians with interquartile ranges (IQRs); these data were analyzed using the Wilcoxon signed-rank test. A p value less than 0.05 was considered statistically significant.

Survey

The survey rationale and an electronic link to the survey were sent by email to 33 Canadian renal pharmacists on July 20, 2021, and the survey remained open for 3 weeks. Responses were anonymous, except that participants were asked to specify the province in which they were practising and whether their organization had an FDI order set or protocol that they were willing to share by email with the research assistant (E.E.). The survey, which took 5–10 minutes to complete, consisted of 18 closed-ended questions with an option for free-text responses to gather information related to FDI use, dosing, administration, monitoring, funding, and safety.

Ordinal data from the closed-ended survey questions were reported as percentages. Qualitative data from the free-text fields were coded and analyzed for themes.

RESULTS

Efficacy and Safety Evaluation

During the 18-month study period, a total of 40 patients (28 with stage 4 or 5 NDD-CKD and 12 receiving PD) received at least 1 infusion of FDI (Table 1). The mean patient age

TABLE 1. Baseline Demographic and Clinical Characteristics of Participants

Characteristic	No. (%) of Participants[a] (n = 40)
Demographic	
Sex	
Male	24 (60)
Female	16 (40)
Age (years) (mean ± SD)	65.6 ± 12.0
Weight (kg) (mean ± SD)	85.2 ± 22.9
Comorbidities	
Diabetes	23 (58)
Hypertension	35 (88)
Cardiac disorders	21 (52)
Subgroups	
Non–dialysis-dependent CKD	28 (70)
eGFR 15–29 mL/min/1.73 m^2 (stage 4)	12 (30)
eGFR < 15 mL/min/1.73 m^2 (stage 5)	16 (40)
Peritoneal dialysis	12 (30)
Clinical	
Hemoglobin (g/L) (mean ± SD)	94.7 ± 15.2
Transferrin saturation[b] (%) (mean ± SD)	14.8 ± 3.8
Ferritin[c] (µg/L) (mean ± SD)	326.8 ± 573.6
Receiving darbepoetin alfa	25 (62)
Cumulative monthly dose[d] (µg) (mean ± SD)	103.2 ± 72.5
Receiving oral iron	26 (65)
Daily dose of elemental iron (mg) (mean ± SD)	233.7 ± 132.0
Receiving IV iron sucrose	7 (17)
Cumulative monthly dose[d] (mg) (mean ± SD)	342.9 ± 378.0

CKD = chronic kidney disease, eGFR = estimated glomerular filtration rate, SD = standard deviation.
[a]Except where indicated otherwise.
[b]Recorded within 3 months before infusion.
[c]Recorded within 6 months before infusion (n = 33).
[d]Dose calculated in the month before initial infusion of ferric derisomaltose.

was 65.6 (SD 12.0) years, and 24 (60%) of the patients were male. At baseline, mean Hgb was 94.7 (SD 15.2) g/L (with 19 patients having Hgb < 95 g/L) and mean TSAT was 14.8% (SD 3.8%). Concomitant medications for treatment of anemia at baseline included oral iron (26 [65%] of the patients) and darbepoetin alfa (25 [63%] of the patients), and 7 patients (17%) were receiving IV iron sucrose during the month before FDI infusion. Additional baseline clinical and demographic characteristics are presented in Table 1.

Thirty-five patients, all of whom received at least 1 FDI infusion, were included in the efficacy analysis. Of the 5 patients who were excluded, 3 had received another form of IV iron during the study period, 1 died for reasons unrelated to the FDI infusion (with no pertinent data available for analysis), and 1 experienced a Fishbane reaction after a partial FDI infusion (Figure 1). A total of 52 infusions of FDI were administered to the 35 included patients over the study period. Forty-eight of the FDI infusions were administered as a single fixed dose of 1000 mg, and the remaining 4 infusions were administered as 2 doses of 500 mg separated by 1 week. Thirteen patients required a second dose of FDI, and 4 patients required a third dose. The median time between the first and second doses was 19.1 (IQR 21.7) weeks and between the second and third doses was 6.6 (IQR 5.7) weeks (Figure 1). Second and third doses were administered to 9 (69%) and 3 (23%) of the 13 patients with stage 5 CKD, respectively. The median duration of study participation was 12.1 (IQR 4.8) months.

Table 2 displays changes from baseline in Hgb, TSAT, and ferritin measured 5.6 to 9.2 weeks after the first FDI infusion for CKD subgroups and all patients combined. For all patients combined, the changes from baseline to first blood work after FDI infusion (the primary efficacy end points) were significant for Hgb (median 9.0 [IQR 13.0] g/L, $p = 0.023$), TSAT (median 11.0 [IQR 11.0] percentage points, $p < 0.001$), and ferritin (271.4 [IQR 272.8] µg/L, $p < 0.001$). The median values for Hgb, TSAT, and ferritin at first blood work after FDI infusion were 104.0 (IQR 19.5) g/L, 25.0% (IQR 10.0%), and 351.4 (IQR 526.6) µg/L, respectively.

The overall effectiveness, as determined by changes from baseline to 3 and 6 months after FDI infusion in Hgb, TSAT, and ferritin for 44 infusions, is outlined in Table 3. Median Hgb increased from 96 g/L at baseline to 106 g/L at 3 months ($p = 0.020$) and returned to 96 g/L at 6 months. There were significant median increases from baseline to the 3-month evaluation in TSAT (from 15% to 23%; $p < 0.001$) and ferritin (from 132.9 µg/L to 294.5 µg/L; $p = 0.027$). Median TSAT remained significantly elevated at 6 months, at 24% ($p < 0.001$). From baseline to 6 months, the median monthly dose of darbepoetin alfa decreased from 80 (IQR 60) µg to 80 (IQR 40) µg ($p < 0.001$), and the median daily dose of oral elemental iron remained relatively unchanged (180 [IQR 161.1] mg versus 300 [IQR 158] mg). The number of patients who required darbepoetin alfa and oral iron declined by 5 and 4, respectively, from baseline to 6 months.

Five patients (mean Hgb 65 g/L, minimum 55 g/L, maximum 72 g/L) received a total of 6 blood transfusions due to gastrointestinal bleeding ($n = 3$ transfusions), postoperative orthopedic complication ($n = 2$ transfusions), or malignancy ($n = 1$ transfusion). Blood transfusion occurred at a median of 60 days after the FDI infusion.

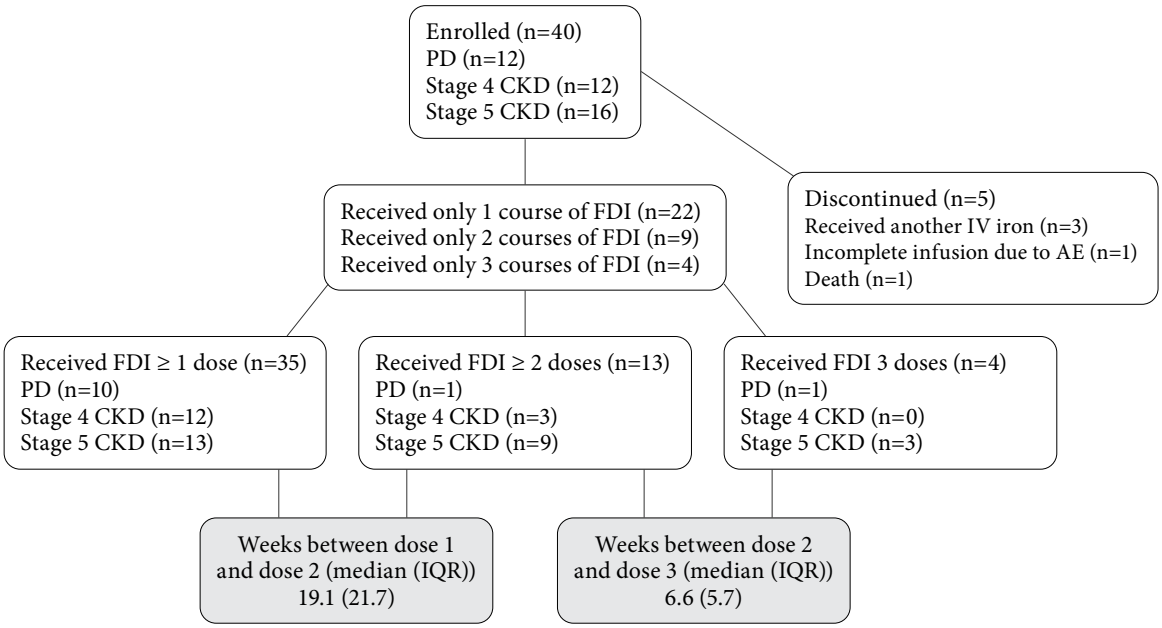

FIGURE 1. Flow diagram for administration of ferric derisomaltose (FDI) to study participants. AE = adverse effect, CKD = chronic kidney disease, PD = peritoneal dialysis. Dosing: FDI 1000 mg ($n = 48$ infusions) or FDI 500 mg × 2, separated by 1 week ($n = 4$ infusions). The median duration of individuals' participation in the study was 12.1 (interquartile range 4.8) months.

TABLE 2. Analysis of Laboratory Parameters after First Ferric Derisomaltose Treatment

Parameter	Patient Group; Median (IQR)			
	CKD Stage 4	CKD Stage 5	Peritoneal Dialysis	Total
Hemoglobin	$n = 12$	$n = 13$	$n = 10$	$n = 35$
Change from baseline to post-treatment (g/L)	5.5 (11.5)	9.0 (17.0)	13.0 (8.0)	9.0 (13.0)
	$p = 0.45$	$p = 0.05$	$p = 0.12$	$p = 0.023$
Time of evaluation (weeks)	5.8 (2.4)	5.9 (3.1)	4.9 (3.2)	5.6 (3.1)
Post-treatment level (g/L)	105.5 (31)	103.0 (11.0)	113.0 (19.4)	104.0 (19.5)
Transferrin saturation	$n = 12$	$n = 13$	$n = 10$	$n = 35$
Change from baseline to post-treatment (percentage points)	10.5 (9.5)	9.0 (14.0)	14.0 (9.5)	11.0 (11.0)
	$p = 0.003$	$p = 0.002$	$p < 0.001$	$p < 0.001$
Time of evaluation (weeks)	6.8 (3.6)	7.1 (3.6)	7.7 (2.1)	7.1 (3.6)
Post-treatment level (%)	24.5 (12.5)	24.0 (9.0)	28.5 (8.2)	25.0 (10.0)
Ferritin	$n = 11$	$n = 8$	$n = 9$	$n = 28$
Change from baseline to post-treatment (µg/L)	273.6 (333.7)	242.2 (165.7)	298.1 (177.9)	271.4 (272.8)
	$p < 0.001$	$p = 0.38$	$p = 0.032$	$p < 0.001$
Time of evaluation (weeks)	8.9 (3.2)	11.0 (3.2)	9.1 (2.9)	9.2 (3.8)
Post-treatment level (µg/L)	387.5 (374.5)	475.8 (593.2)	330.3 (328.8)	351.4 (526.6)

CKD = chronic kidney disease, IQR = interquartile range.

TABLE 3. Overview of Effectiveness of Ferric Derisomaltose during 6-Month Follow-Up Period[a]

Parameter and Visit[b]	*n*	Mean ± SD	Minimum	Median (IQR)	Maximum
Hemoglobin (g/L)					
Baseline	35	95.5 ± 14.8	59	96 (19)	127
Midpoint	32	103.7 ± 17.4	54	106 (19)[c]	137
Final	30	97.8 ± 15.3	65	96 (18.3)	148
Difference	NA	2.3 ± 0.5	6	0 (17)	21
Transferrin saturation (%)					
Baseline	35	14.9 ± 3.8	8	15 (4)	24
Midpoint	30	25.3 ± 10.5	9	23 (11)[c]	51
Final	30	23.4 ± 11.0	11	24 (11.8)[c]	61
Difference	NA	8.5 ± 7.2	3	7 (15)	37
Ferritin (µg/L)					
Baseline	31	358.0 ± 586.9	15.1	132.9 (337.5)	2469.5
Midpoint	24	622.4 ± 924.0	7.1	294.5 (621.1)[c]	4018.5
Final	20	407.8 ± 442.0	9.8	270.9 (321.8)[d]	1985.2
Difference	NA	120.1 ± 14.2	–5.3	174.7 (131.4)	–484.3
Monthly darbepoetin alfa dose (µg)					
Baseline	20	108.0 ± 80.4	40	80 (60)	400
Midpoint	16	93.8 ± 49.4	20	80 (45)[c]	200
Final	15	94.7 ± 60.2	40	80 (40)[c]	240
Difference	NA	–13.3 ± 20.2	0	0 (20)	–160
Daily oral elemental iron dose (mg)					
Baseline	24	232.6 ± 137.9	60	180 (161.1)	600
Midpoint	19	237.7 ± 124.1	60	300 (150.3)	600
Final	20	236.7 ± 125.3	60	300 (158)	600
Difference	NA	4.1 ± 12.6	0	0 (0)	0

IQR = interquartile range, NA = not applicable.
[a]Includes data related to 44 infusions of ferric derisomaltose (35 at baseline, 39 by the midpoint, 44 by final), with all but 1 infusion completed more than 30 days before the blood work.
[b]Midpoint = 3 months, final = 6 months; difference refers to change from baseline to 6 months.
[c]Statistically significant difference from baseline to midpoint or final evaluation, $p < 0.05$.
[d]$p = 0.08$.

Three patients, all of whom received a fixed dose of 1000 mg infused over 20 minutes, experienced nonsevere adverse reactions to FDI. Two of the reactions were classified as isolated, and one was deemed to be a Fishbane reaction; the rates of these types of reactions were 5% and 3%, respectively. There were no anaphylactic reactions. The management of adverse reactions and subsequent rechallenge with IV iron are outlined in Table 4.

Survey

Twenty-three (70%) of the 33 Canadian renal pharmacists participated in the electronic survey, with at least 1 participant from each province. FDI was funded by the province (17 respondents [74%]) or listed on the hospital drug formulary (15 respondents [65%]). The most commonly reported patient populations for whom funding was approved by the province or the hospital were patients with NDD-CKD (15/19 [79%] and 13/17 [76%] respondents, respectively), patients receiving PD (14/19 [74%] and 12/17 [71%] respondents, respectively), and patients undergoing home hemodialysis (12/19 [63%] and 8/17 [47%] respondents, respectively). Most respondents (16/20 [80%]) reported that FDI is administered in a hospital outpatient unit, clinic, or facility, with administration in a private infusion clinic or renal program clinic reported by 2/20 respondents (10%). No respondents reported self-administration of FDI by patients undergoing home hemodialysis. The most commonly reported FDI dose was 1000 mg IV infusion (15/19 [79%]), followed by 500 mg (12/19 [63%]) and 1500 mg (7/19 [37%]). The reported administration time for FDI infusion ranged from 20 to 65 minutes. Only 1 respondent reported administering FDI 500 mg as an IV bolus over 2 minutes.

Eleven (52%) of the 21 respondents reported using an FDI order set. Participants reported that subsequent doses of FDI were based on iron indices obtained either 4 weeks after infusion (15/21 respondents [71%]) or before the next clinic visit (i.e., at 2–3 months) (6/21 respondents [29%]). No participants reported using an FDI protocol for subsequent dosing, because of limited experience or because no data were available. Of the 16 participants who described their management of a Fishbane reaction with FDI, 7 (44%) reported waiting 30 minutes and restarting the FDI infusion at a slower rate, 8 (50%) reported switching to a different IV iron preparation for the next dose, and 1 (6%) reporting rechallenge with FDI at a later date.

DISCUSSION

This study demonstrated significant improvements in median Hgb, TSAT, and ferritin measured a mean of 7.3 weeks from baseline in NDD-CKD (stage 4 or stage 5) and PD patients who received 1 course of FDI 1000 mg. In terms of the overall effectiveness by 3 months after FDI infusion, median increases in Hgb, TSAT, and ferritin were statistically significant. Although Hgb peaked at 3 months and returned to near-baseline levels by 6 months, TSAT and ferritin remained elevated at 6 months and were within their respective guideline targets. The FERWON-EXT trial similarly reported a peak effect for Hgb at 3 months after FDI treatment.[19] European NDD-CKD and PD trials evaluating FDI showed comparable significant improvements in Hgb, TSAT, and ferritin from baseline to various post-FDI time points (between 4 and ≥ 52 weeks).[14-17,19,20]

Our study revealed a significant and clinically relevant reduction in the median monthly dose of darbepoetin alfa, as well as a reduction in the number of patients requiring ESA treatment, from baseline to 3 and 6 months. A significant mean reduction in the use of ESA (specifically epoetin alfa) was also reported in a 9-month FDI study.[14] An ESA-sparing effect has potential benefits, including lowering the ESA-associated risk for stroke or cardiovascular events, as well as reducing the economic burden of ESA therapy.[30] Although we did not evaluate the cost-effectiveness of FDI relative to other IV irons, a reduction in the number of FDI infusions per patient has been shown to translate into economic savings in the United Kingdom.[31]

The median interval between FDI infusions was 19.1 weeks between doses 1 and 2 and 6.6 weeks between doses 2

TABLE 4. Summary of Adverse Effects[a] after Infusion of Ferric Derisomaltose and Management

Reaction Type	Symptoms	Time of Symptom Onset (min)[b]	Reaction Management	IV Iron Rechallenge
Isolated[c] (n = 1 patient)	Nausea and retching	30	Administered dimenhydrinate 50 mg IV	No
Isolated[c] (n = 1 patient)	Nausea and vomiting	60	Administered dimenhydrinate 25 mg IV	No
Fishbane[d] (n = 1 patient)	Abdominal pain	15–30	Stopped infusion, administered acetaminophen 650 mg PO	Yes, iron sucrose

[a]All reactions occurred with ferric derisomaltose 1000 mg IV infusion over 20 minutes (administered to a total of 40 patients).
[b]Time in minutes after infusion was started.
[c]Non–life-threatening symptoms affecting 1 organ system, excluding the respiratory system.[29]
[d]The Fishbane reaction can consist of transient flushing, truncal myalgia, and tightness or pain in the chest and back.[29]

and 3. For those needing a second dose, these findings suggest that retreatment correlates with infusion of FDI 1000 mg IV every 5 months. The NIMO-CKD-UK trial reported that the probability of FDI retreatment was higher among those who received FDI doses at or below 1000 mg (mean 814.4 mg; group 1) than among those who received FDI doses above 1000 mg (mean 1537 mg; group 2).[17] Although the mean FDI dose was lower in group 1 of the earlier study than in our study (814.4 mg versus 1000 mg, respectively), the proportions of participants requiring 1 dose (75%) or 2 doses (25%) were similar to our findings (22/35 [63%] and 9/35 [26%], respectively).

In our study, the follow-up period was variable, and for some it was intentionally longer than 12 months, in order to include more infusions for determination of adverse effects. Three (8%) of the 40 patients had mild reactions, which resolved a median of 30 minutes after the infusion. The safety profile of FDI observed in our study was consistent with the findings of other clinical trials.[14-20] In a recently conducted evaluation of severe hypersensitivity reactions in 21 randomized controlled trials of IV irons, a mean odds ratio of 0.51 was reported for FDI compared with iron sucrose, indicating a 49% lower risk of experiencing a serious reaction with FDI.[22]

In the survey of renal pharmacists, at least 65% of respondents reported that their province and/or hospital provided funding to use FDI primarily in NDD-CKD, PD, and home hemodialysis populations. Given that the most commonly administered FDI dose is 1000 mg IV infusion, the retreatment interval observed in our study provides a useful guide for clinicians. None of the survey respondents reported using an FDI protocol similar to the protocols commonly used for iron sucrose or sodium ferric gluconate.[24-27]

This study had several strengths. It provides real-world Canadian evidence of the efficacy and safety of FDI in NDD-CKD and PD patients, as well as useful information for clinicians about the timing of subsequent doses of FDI and initial data to support the development of an FDI protocol. To the authors' knowledge, this is the first Canadian study providing initial retreatment information that may aid in the development of an FDI protocol.

Despite these strengths, there were some limitations. First, we were dependent on patients completing blood work during a period when the availability of laboratory testing was limited by the COVID-19 pandemic; this resulted in a delay in laboratory evaluations to a median of 5.6 to 9.2 weeks after the FDI injection (whereas the usual standard is 4 to 6 weeks). To accommodate this limited testing availability, we included values within 45 days on either side of the 3- and 6-month evaluation points. Second, we emulated the actual clinical setting with participants representative of typical NDD-CKD and PD populations and did not exclude patients who had received a blood transfusion. Given that these patients had mean Hgb of 65 g/L, it is likely that their inclusion resulted in less favourable laboratory values after FDI. Third, ferritin data were available for only 20 patients at the 6-month evaluation, because our program relies mainly on TSAT. Fourth, the FDI dosing interval was influenced by availability of the infusion chair, not only the prescribed dosing interval. Fifth, a small number of patients had a follow-up period that was substantially shorter than the intended 18 months (as indicated by the overall median of 12.1 months). If all of these patients had been followed for 18 months, there likely would have been more FDI infusions to evaluate for effectiveness and safety. Finally, we did not determine whether FDI reduces the cost of care relative to IV iron formulations currently in use for these populations; this issue requires further study.

CONCLUSION

This study provides supportive evidence that FDI is an effective and safe treatment for anemia in patients with NDD-CKD and those undergoing PD. Our findings could be used to inform the development and evaluation of FDI dosing protocols in the future.

References

1. Gotloib L, Silverberg D, Fudin R, Shostak A. Iron deficiency is a common cause of anemia in chronic kidney disease and can often be corrected with intravenous iron. *J Nephrol.* 2006;19(2):161-7.
2. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. *PLoS One*. 2014;9(1):e84943.
3. Batchelor EK, Kapitsinou P, Pergola PE, Kovesdy CP, Jalal DI. Iron deficiency in chronic kidney disease: updates on pathophysiology, diagnosis, and treatment. *J Am Soc Nephrol*. 2020;31(3):456-68.
4. Eriksson D, Goldsmith D, Teitsson S, Jackson J, van Nooten F. Cross-sectional survey in CKD patients across Europe describing the association between quality of life and anaemia. *BMC Nephrol*. 2016; 17(1):97.
5. Dowling TC. Prevalence, etiology, and consequences of anemia and clinical and economic benefits of anemia correction in patients with chronic kidney disease: an overview. *Am J Health Syst Pharm*. 2007; 64(13 Suppl 8):S3-7.
6. Shepshelovich D, Rozen-Zvi B, Avni T, Gafter-Gvili A. 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(5):677-90.
7. McMurray JJV, Parfrey PS, work group co-chairs. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int Suppl*. 2012;2(4):279-335.
8. Moist LM, Troyanov S, White CT, Wazny LD, Wilson JA, McFarlane P, et al. Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for anemia in CKD. *Am J Kidney Dis*. 2013;62(5):860-73.
9. Macdougall IC, Bock AH, Carrera F, Eckardt KU, Gaillard C, Van Wyck D, et al.; FIND-CKD Study Investigators. 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(11):2075-84.
10. Johnson DW, Herzig KA, Gissane R, Campbell SB, Hawley CM, Isbel NM. Oral versus intravenous iron supplementation in peritoneal dialysis patients. *Perit Dial Int*. 2001;21 Suppl 3:S231-5.
11. Ferric derisomaltose [product monograph]. Pfizer Canada ULC; 2018 Jun 22.

12. Jahn MR, Andreasen HB, Fütterer S, Nawroth T, Schüemann V, Kolb U, et al. A comparative study of the physicochemical properties of iron isomaltoside 1000 (Monofer), a new intravenous iron preparation and its clinical implications. *Eur J Pharm Biopharm*. 2011;78:480-91.
13. Wikström B, Bhandari S, Barany P, Kalra PA, Ladefoged S, Wilske J, et al. Iron isomaltoside 1000: a new intravenous iron for treating iron deficiency in chronic kidney disease. *J Nephrol*. 2011;24(5):589-96.
14. Biggar P, Leistikow F, Walper A. A prospective observational study of effectiveness and safety of iron isomaltoside in patients with chronic renal failure and iron deficiency anemia. *Clin Nephrol*. 2016;86(6):310-8.
15. Kalra PA, Bhandari S, Saxena S, Agarwal D, Wirtz G, Kletzmayr J, et al. A randomized trial of iron isomaltoside 1000 versus oral iron in non-dialysis-dependent chronic kidney disease patients with anaemia. *Nephrol Dial Transpl*. 2016;31(4):646-55.
16. Kalra PA, Bhandari S. Efficacy and safety of iron isomaltoside (Monofer®) in the management of patients with iron deficiency anemia. *Int J Nephrol Renovasc Dis*. 2016;9:53-64.
17. Kalra PA, Bhandari S, Spyridon M, Davison R, Lawman S, Mikhail A, et al. NIMO-CKD-UK: a real-world, observational study of iron isomaltoside in patients with iron deficiency anaemia and chronic kidney disease. *BMC Nephrol.* 2020;21:539.
18. Bhandari S, Kalra PA, Berkowitz M, Belo D, Thomsen LL, Wolf M. Safety and efficacy of iron isomaltoside 1000/ferric derisomaltose versus iron sucrose in patients with chronic kidney disease: the FERWON-NEPHRO randomized, open-label, comparative trial. *Nephrol Dial Transplant*. 2021;36(1):111-20.
19. Achebe MM, Glaspy J, Kalra PA, Auerbach M, Thomsen LL, Chandari S. A 6 month extension trial evaluating safety and efficacy of ferric derisomaltose in patients with iron deficiency anemia: the FERWON-EXT trial. *Am J Hematol*. 2020;95(10):E276-9.
20. Jensen G, Gøransson L, Fernström A, Furuland H, Christensen JH. Treatment of iron deficiency in patients with chronic kidney disease: a prospective observational study of iron isomaltoside (NIMO Scandinavia). *Clin Nephrol*. 2019;39(2):246-53.
21. Sivakumar C, Jubb VM, Lamplugh A, Bhandari S. Safety of intravenous iron — Cosmofer and Monofer therapy in peritoneal dialysis and non-dialysis dependent chronic kidney disease patients. *Perit Dial Int*. 2019;39(2):192-5.
22. Pollock RF, Biggar P. Indirect methods of comparison of the safety of ferric derisomaltose, iron sucrose and ferric carboxymaltose in the treatment of iron deficiency anemia. *Expert Rev Hematol.* 2020; 13(2):187-95.
23. Feraheme (ferumoxytol) – Important changes to the delivery and new restrictions on the use due to information on serious allergic reactions – for health professionals. Government of Canada; 2014 [cited 2022 Jan 12]. Available from: https://healthycanadians.gc.ca/recall-alert-rappel-avis/hc-sc/2014/42607a-eng.php?_ga=1.244811781.1649916231.1487795227
24. *Nurse or pharmacist-led anemia management protocol educational package*. Canadian Kidney Knowledge Translation and Generation Network; 2015 [cited 2022 Jan 24]. Available from: https://www.cann-net.ca/images/CANN-NET_Anemia_Management_Protocol_Educational__Policy_Documents_April_7_2015.pdf
25. *Peritoneal dialysis anemia management protocol*. BC Renal; 2021 [cited 2022 Jan 24]. Available from: http://www.bcrenal.ca/resource-gallery/Documents/Peritoneal_Dialysis_Anemia_Management_Protocol.pdf
26. *CKD non-dialysis anemia management protocol*. BC Renal; 2021 [cited 2022 Jan 24]. Available from: http://www.bcrenal.ca/resource-gallery/Documents/CKD_Non-Dialysis-Anemia_Management_Protocol.pdf
27. Intravenous iron for chronic kidney disease order sheet. Manitoba Renal Program; 2020 [cited 2022 Jan 24]. Available from: https://www.kidneyhealth.ca/files/orders/W-00495.pdf
28. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP; STROBE Initiative. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *PLoS Med*. 2007;4(10):e296.
29. Lim W, Afif W, Knowles S, Lim G, Lin Y, Mothersill C, et al. Canadian expert consensus: management of hypersensitivity reactions to intravenous iron in adults. *Vox Sang*. 2019;114(4):363-73.
30. Palmer SC, Navaneethan SD, Craig JC, Johnson DW, Tonelli M, Garg AX, et al. Meta-analysis: erythropoiesis-stimulating agents in patients with chronic kidney disease. *Ann Intern Med.* 2010;153(1):23-33.
31. Pollock RF, Muduma G. A budget impact analysis of parenteral iron treatments for iron deficiency anemia in the UK: reduced resource utilization with iron isomaltoside 1000. *Clinicoecon Outcomes Res*. 2017; 9:475-83.

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