International Journal of Nephrology and Renovascular Disease

Dovepress

open access to scientific and medical research

Open Access Full Text Article

REVIEW

Efficacy and safety of iron isomaltoside (Monofer®) in the management of patients with iron deficiency anemia

This article was published in the following Dove Press journal:
International Journal of Nephrology and Renovascular Disease
10 March 2016
Number of times this article has been viewed

Philip A Kalra[1]
Sunil Bhandari[2,3]

[1]Department of Renal Medicine, Salford Royal NHS Foundation Trust, Salford, UK; [2]Hull and East Yorkshire Hospitals NHS Trust, Hull, UK; [3]Hull York Medical School, Hull, UK

Abstract: New intravenous (IV) iron preparations should ideally be capable of delivering a wide dosing range to allow iron correction in a single or low number of visits, a rapid infusion (doses up to 1,000 mg must be administered over more than 15 minutes and doses exceeding 1,000 mg must be administered over 30 minutes or more), and minimal potential side effects including low catalytic/labile iron release with minimal risk of anaphylaxis. Furthermore, they should be convenient for the patient and health-care professional, and cost effective for the health-care system. The intention behind the development of iron isomaltoside (Monofer®) was to fulfill these requirements. Iron isomaltoside has been shown to be effective in treating iron deficiency anemia across multiple therapeutic patient groups and compared to placebo, IV iron sucrose, and oral iron. Iron isomaltoside consists of iron and a carbohydrate moiety where the iron is tightly bound in a matrix structure. It has a low immunogenic potential, a low potential to release labile iron, and does not appear to be associated with clinically significant hypophosphatemia. Due to the structure of iron isomaltoside, it can be administered in high doses with a maximum single dosage of 20 mg/kg body weight. Clinical trials and observational studies of iron isomaltoside show that it is an effective and well-tolerated treatment of anemia across different therapeutic areas with a favorable safety profile.

Keywords: iron deficiency anemia, iron isomaltoside, high dose, iron treatment, hypophosphatemia, intact fibroblast growth factor 23

Introduction

Iron deficiency anemia (IDA) is a common problem associated with many chronic disorders including chronic kidney disease (CKD). The major causes of anemia in patients with CKD are iron and erythropoietin deficiencies and a decreased responsiveness to the actions of erythropoietin.[1]

Anemia is generally associated with reduced quality of life (QoL), progression of disease, and poorer outcomes,[1–3] and therefore treatment of the underlying cause of anemia should have a high priority.

Intravenous (IV) iron offers a rapid and efficient means of iron correction, and it is superior to oral iron therapy in many circumstances.[4] Treatment with oral iron may be adequate for some patients, but intolerance, abnormal absorption due to inflammation, noncompliance, and large iron deficits may lead to an inadequate treatment of the anemia with oral iron.[5] International guidelines recommend IV iron preparations as the preferred option in the correction of IDA in several of these circumstances and when there is a high iron demand, since it is more effective, better tolerated, and improves QoL to a greater extent than oral iron supplements.[4,6,7]

Correspondence: Philip A Kalra
Department of Renal Medicine, Salford Royal NHS Foundation Trust, Stott Lane, Salford M6 8HD, UK
Tel +44 161 206 0509
Fax +44 161 206 5713
Email philip.kalra@srft.nhs.uk

submit your manuscript | www.dovepress.com
Dovepress
http://dx.doi.org/10.2147/IJNRD.S89704

Iron isomaltoside 1000 (Monofer®; Pharmacosmos A/S, Holbaek, Denmark) was introduced in Europe in 2010. It consists of iron and a carbohydrate moiety where the iron is tightly bound in a matrix structure. This enables a controlled and slow release of iron to iron-binding proteins, avoiding potential toxicity from release of labile iron. Isomaltoside 1000 is an oligosaccharide with a mean molecular weight of 1,000 Da, which consists predominantly of chains corresponding to 3–5 glucose units. In contrast to the branched dextran polysaccharides present in iron dextran, isomaltoside 1000 is linear and unbranched.[8] The strongly bound iron within the iron isomaltoside formulation allows flexible dosing, including high dosing (single doses of 1–2 g) over a short time period. Compared to compounds in which iron is more loosely bound in the complex, the iron isomaltoside complex potentially leads to generation of less oxidative stress and less immunological toxicity.[9,10]

In the European Union, iron isomaltoside can be administered with a maximum single dosage of 20 mg/kg actual body weight.[11] The dose flexibility and possibility of providing full iron correction over a short time period in one visit make iron isomaltoside highly convenient for both the health-care professionals and patients. In this paper, we review current data regarding pharmacology, efficacy, and safety of iron isomaltoside.

Pharmacological and pharmacokinetic properties

Following IV administration, iron isomaltoside is rapidly taken up by the cells in the reticuloendothelial system (RES), particularly in the liver and spleen, from where iron is slowly released for use. The plasma half-life is 20–32 hours.[12,13] Circulating iron isomaltoside is removed from the plasma by cells of the RES, which split the complex into iron and isomaltoside. The isomaltoside moiety is either metabolized or excreted. Iron is immediately bound and stored, mainly in ferritin. The iron replenishes hemoglobin (Hb) and depleted iron stores[11] as well as being important for many biological processes including the electron transport chain and tricarboxylic acid cycle. Two pharmacokinetic (PK) trials have been published.

A prospective, open-label, randomized PK trial of iron isomaltoside in CKD was conducted at a single center in the USA. The trial aimed at assessing PK properties (*s*-iron) of iron isomaltoside in patients with CKD stage 5D (hemodialysis). A total of 18 patients (12 men, six women) were randomized 1:1:1 to 100, 200, and 500 mg IV bolus treatment. The trial demonstrated an expected increase in the levels of total *s*-iron with escalating doses of iron isomaltoside from the time of drug administration to 7 days postdose. Hence, the PK data showed a dose-dependent increase in area under serum concentration–time curve and maximum serum concentration (C_{max}), with no difference in elimination rate constant (K_e) and half-life ($T_{1/2}$) between the 100, 200, and 500 mg IV bolus doses of iron isomaltoside. The $T_{1/2}$ was between 28.86 and 31.14 hours, and time to reach maximum concentration (T_{max}) was between 0.57 and 1 hour.[13]

A second open-label, single-center, crossover PK trial was performed in 12 patients (five men, seven women) with inflammatory bowel disease (IBD).[12] The patients were allocated to one of two single-dose treatments where iron isomaltoside was administered as a single bolus dose of 100 or 200 mg with a 4-week interval between the two doses. PK variables were analyzed for total iron (TI), isomaltoside-bound iron (IBI), and transferrin-bound iron (TBI) according to a one-compartment model. IBI was calculated by subtracting TBI from TI, assuming that no labile, catalytic, or non-transferrin-bound iron was present and that quantities of ferritin were negligible, so that the only iron forms present in plasma were TI, TBI, and IBI. The concentration versus time relationship for IBI and TI showed first-order kinetics (the elimination was directly proportional to the drug concentration) with small deviations for dose-linearity, and the PK parameters for IBI were close to that of TI. Thus, TI could be used as a marker of iron isomaltoside PK in future PK trials. Only 1% of the doses administered were excreted in the urine.[12]

Efficacy and safety trials

Several clinical trials, mainly short term, have been reported for iron isomaltoside where it has been shown to be well tolerated and to improve markers of IDA in patients receiving dialysis,[14,15] those with nondialysis-dependent chronic kidney disease (NDD-CKD),[16] those with chronic heart failure (CHF),[17] IBD,[18–20] and underlying cancer,[21] those undergoing cardiac surgery,[22] and women with postpartum hemorrhage.[23] The trial design, dosing regimen, patient groups, and main results of the trials are summarized in Table 1.

Iron isomaltoside administered to patients with CKD

Wikström et al[14] investigated patients with NDD-CKD or stage 5D CKD who were either iron naïve or prepared to switch their usual IV iron therapy. The primary endpoint was establishment of a safety profile of iron isomaltoside in CKD patients, whereas efficacy was the secondary endpoint. In total, 584 treatments were given (523 IV bolus 100 mg, 17 IV bolus

100–200 mg, and 44 high-dose infusions) with single doses up to 1,800 mg.[24] Hb, transferrin saturation, and ferritin increased significantly, and no acute hypersensitivity reaction or delayed allergic reactions were reported. It was concluded that iron isomaltoside administered to CKD patients as repeated bolus injections or single high-dose infusion was well tolerated and resulted in improved markers of iron status and anemia.[14]

In an open-label randomized clinical trial of NDD-CKD patients by Kalra et al,[16] the primary objective was to compare IV iron isomaltoside to oral iron sulfate in reducing renal-related anemia, evaluated as the ability to increase Hb. Iron isomaltoside was noninferior to iron sulfate in increasing Hb from baseline to week 4 in both the full analysis set and per protocol analysis set ($P<0.001$). In addition, iron isomaltoside showed superiority over iron sulfate with significantly higher increases in Hb concentration from baseline to week 4 (full analysis set: $P=0.039$; per protocol: $P=0.047$). It was concluded that iron isomaltoside was more efficacious than oral iron in increasing Hb and proved to be better tolerated than oral iron at the tested dose levels in NDD-CKD patients.[16]

In 2015, Bhandari et al[15] demonstrated noninferiority of IV iron isomaltoside to IV iron sucrose, determined as the ability to maintain Hb between 9.5 and 12.5 g/dL ($P=0.01$) in patients with CKD receiving hemodialysis. It was concluded that iron isomaltoside and iron sucrose have comparative efficacy in maintaining Hb concentrations in this population and that both preparations were well tolerated with a similar short-term safety profile.[15]

At the 52nd Congress of the European Renal Association – European Dialysis and Transplantation Association (ERA-EDTA), May 2015, Leistikow et al[25] presented an observational study investigating the treatment routine, efficacy, safety, and tolerability of iron isomaltoside in CKD patients. The patients each received a mean of 2,413 mg iron isomaltoside during the observation period, and as it was often administered in high single iron doses it took only a few visits to cover the cumulative iron need. A total of 525 patients were concomitantly treated with erythropoiesis-stimulating agents (ESAs), but the proportion of patients treated with ESA decreased significantly with iron isomaltoside administration ($P<0.002$). It was concluded that iron isomaltoside is a cost-effective IV iron therapy decreasing the need for ESAs; iron isomaltoside was well tolerated.[25]

Iron isomaltoside administered to patients with IBD

Reinisch et al[18] evaluated the efficacy of iron isomaltoside versus oral iron in reducing IDA, evaluated as the ability to increase Hb at week 8 in patients with IBD and IDA. The mean cumulative dose of iron isomaltoside in the infusion and the bolus groups was 885 mg (SD: 238 mg, range: 195–1,500 mg) and 883 mg (SD: 296 mg, range: 350–2,500 mg), respectively. Noninferiority could not be demonstrated with respect to the primary endpoint. As the mean cumulative Ganzoni calculated iron isomaltoside dose administered was not more than 885 mg, the authors suggested that the calculation itself might have led to an underestimation of the required iron dose. Indeed, patients receiving >1,000 mg iron isomaltoside (mean: 1,313 mg) had a response rate (Hb increase of ≥2 g/dL) of 93% ($P>0.001$ when compared with oral iron). In trials with other IV iron compounds in IBD patients, the mean cumulative dosages have been higher.[26,27] Thus, the authors suggested that the cumulative IV dosing may have been too low in this trial, which harmonizes with Gozzard's[28] findings that doses of up to 3,600 mg iron are required in anemic IBD patients to correct the deficit.

In 2015, Reinisch et al[18,19] reported a 1-year extension trial of this IBD trial[18] evaluating the need for additional IV iron isomaltoside doses to maintain a stable Hb.[19] In patients with Hb ≥12.0 g/dL at baseline; 74% were able to maintain their Hb ≥12.0 g/dL during 1 year. The authors concluded that repeated treatment of iron deficiency (ID) with iron isomaltoside could avoid episodes of IDA without major safety issues.[19]

Dahlerup and Lindgren[20] presented a prospective, open-label, multicenter trial conducted in 21 patients with IBD and IDA. The authors concluded that infusions of high-dose IV iron isomaltoside, administered as single doses of up to 2,000 mg and cumulative doses of up to 3,000 mg over a short duration, were completed without safety concerns and were efficacious in increasing Hb levels in patients with IBD.[20]

Frigstad et al[29] presented an observational study in which they investigated the treatment strategy, efficacy, and safety of iron isomaltoside administered to 149 IBD patients. Although the patients had significant increases in Hb and iron parameters ($P<0.001$), more than 25% of the patients were still anemic after one iron treatment, again suggesting that IBD patients probably receive inadequate iron dosing in routine clinical practice.[29]

Iron isomaltoside administered to cancer patients with anemia

Birgegård et al[21] presented an open-label randomized clinical trial in anemic cancer patients which compared the efficacy of IV iron isomaltoside to oral iron sulfate, determined as change in Hb from baseline to week 4. Iron isomaltoside

Table 1 Overview of trials with iron isomaltoside

Trial design	Dosing regimen	Main inclusion criteria	Number of patients	Duration	Main efficacy results		Main safety results	Reference
					Hemoglobin	Other findings		
Chronic kidney disease (CKD); dialysis and nondialysis								
Open-label, noncomparative trial	The Ganzoni formula was used for calculating the iron need Iron isomaltoside was administered as four repeated bolus injections of 100–200 mg or a high single full iron repletion dose	CKD patients (dialysis or nondialysis): 1. Currently treated with parenteral iron and had an Hb level ≤11.0 g/dL 2. Willing to switch their current parenteral iron and had an Hb level ≤13.0 g/dL 3. Ferritin <800 µg/L	182	8 weeks	Mean (SD) Hb increased from 9.9 (0.9) g/dL at baseline to 11.1 (1.5) g/dL at week 8 in patients not previously having received IV iron ($P<0.001$) and remained stable in patients receiving maintenance iron therapy (11.5 [1.0] g/dL at baseline, 11.8 [1.2] g/dL at week 8; $P=0.05$)	TSAT and ferritin increased significantly from baseline to week 8 ($P<0.001$)	Nineteen ADRs were reported of which two were serious. The two serious ADRs were sepsis with *Staphylococcus aureus* and unstable angina, neither of which were directly attributed to iron administration. No acute hypersensitivity reaction or delayed allergic reactions were reported	14
Observational study	Iron isomaltoside was administered according to usual daily clinical practice and in accordance with the authorized indication	Dialysis and NDD-CKD patients with CKD stage 3–5	695	9 months	Mean (SD) Hb increased from 11.0 (1.7) to 11.6 (1.6) g/dL ($P<0.0001$)	Ferritin and TSAT increased significantly ($P<0.0001$). The proportion of patients treated with ESA decreased significantly when the patients received iron isomaltoside ($P<0.002$)	No ADR was reported	25
Chronic kidney disease; nondialysis								
Open-label, randomized, comparative, noninferiority trial	An adapted Ganzoni formula was used for calculating the iron need. Iron isomaltoside was administered as maximum 1,000 mg as single doses or bolus injections of 500 mg once weekly Oral iron was administered as 200 mg daily for 8 weeks	Nondialysis-dependent CKD patients: 1. Hb <11.0 g/dL 2. Ferritin <200 µg/L and/or TSAT <20% 3. Not receiving ESA treatment	351	8 weeks	Iron isomaltoside was noninferior to iron sulfate in its ability to increase Hb from baseline to week 4 ($P<0.001$). In addition, iron isomaltoside also showed superiority over oral iron ($P<0.05$)	There was a statistically significant increase in both ferritin and TSAT and a decrease in total iron-binding capacity from baseline to week 8 in the IV iron group compared with the oral iron group ($P<0.01$)	ADRs were observed in 10.5% of the patients in the IV iron group and in 10.3% of the patients in the oral iron group. Three serious ADRs were reported. All patients fully recovered. More patients treated with oral iron sulfate were withdrawn from the trial due to AEs (4.3 versus 0.9% patients)	16

Chronic kidney disease, hemodialysis								
Open-label, randomized, comparative, noninferiority trial	Iron isomaltoside was administered either as a single bolus injection of 500 mg or as 500 mg split bolus doses of 100, 200, and 200 mg Iron sucrose was administered as 500 mg split bolus doses of 100, 200, and 200 mg	CKD patients in hemodialysis: 1. Hb between 9.5 and 12.5 g/dL 2. Ferritin <800 µg/L 3. TSAT <35% 4. Stable ESA treatment	351	6 weeks	The majority (>82%) of patients treated with either iron isomaltoside or iron sucrose were able to maintain Hb between 9.5 and 12.5 g/dL at week 6, and iron isomaltoside showed to be noninferior to iron sucrose (P=0.01)	Ferritin increased significantly from baseline to weeks 1, 2, and 4 in the iron isomaltoside group compared with the iron sucrose group (P<0.01)	ADRs were observed in 5.2% of the patients in the iron isomaltoside group and 2.6% of the patients in the iron sucrose group. Three serious ADRs were reported (one event of hypersensitivity in the iron isomaltoside group [1/230, 0.4%], and one staphylococcal bacteremia and one event of dyspnea [treated as a hypersensitivity reaction] in the iron sucrose group [2/114, 1.8%])	15
Inflammatory bowel disease (IBD)								
Open-label, randomized, comparative, noninferiority trial	An adapted Ganzoni formula was used for calculating the iron need. Iron isomaltoside was administered as maximum 1,000 mg as single doses or bolus injections of 500 mg once weekly Oral iron was administered as 200 mg daily for 8 weeks	IBD patients: 1. Score of ≤5 on the Harvey–Bradshaw index for Crohn's disease or a partial Mayo score of ≤6 for ulcerative colitis 2. Hb <12 g/dL 3. TSAT <20%	338	8 weeks	Noninferiority could not be demonstrated due to an underestimation of the required iron dose. Patients receiving >1,000 mg iron isomaltoside had a response rate (Hb increase of ≥2g/dL) in 93% (P>0.001 when compared with oral iron)	There was an improvement in QoL from baseline to weeks 4 and 8 within each treatment group	ADRs were observed in 14% of the patients in the IV iron group and 10% of the patients in the oral iron group. Four patients in the IV iron group experienced nonserious ADRs reported as hypersensitivity. All four patients fully recovered	18
Open-label extension trial	The patients were allowed re-dosing with 500–2,000 mg single-dose infusions based on Hb, TSAT, ferritin, and body weight	IBD patients: 1. Who completed the lead-in trial or 2. Discontinued from the lead-in trial due to intolerance to oral iron	39	12 months	In patients with Hb ≥12.0 g/dL at baseline; 74% were able to maintain their Hb ≥12.0 g/dL during the year	A total of 68 doses were given to 34 patients (five patients did not need any redosing) and 81% of these doses were ≥1,000 mg and 34% were ≥1,500 mg. The mean cumulative dose per patient over 1 year was 2,192 mg (range: 30–7,000 mg)	Two nonserious ADRs (hypersensitivity) were reported. Both patients fully recovered	19

(*Continued*)

Table 1 (*Continued*)

Trial design	Dosing regimen	Main inclusion criteria	Number of patients	Duration	Main efficacy results		Main safety results	Reference
					Hemoglobin	Other findings		
Open-label safety trial	Based upon Hb and body weight, the patients were divided into two treatment groups; Group A: total dose of 1,500 mg (single infusion) or 2,000 mg (in one or two infusions(s)) of IV iron isomaltoside Group B: total dose of 2,500 or 3,000 mg IV in two infusions	IBD patients: 1. Hb <12 g/dL for women and Hb <13 g/dL for men 2. Patients with CRP above the ULN of normal had to have a ferritin <100 µg/L; patients with a CRP ≤ ULN had to have a ferritin <30 µg/L	21	8 or 16 weeks	There was a significant increase in Hb at all time points within both treatment groups ($P<0.05$)	There was a significant increase in TSAT at all time points within both treatment groups ($P<0.05$) Ferritin increased significantly at all time points in patients dosed with 1,500 or 2,000 mg (group A) ($P<0.001$)	Four patients experienced nine ADRs. In all cases, the patients fully recovered	20
Observational study	Iron isomaltoside was administered according to two different calculations: 1. simplified dosing approach or 2. Ganzoni formula	IBD patients	149	–	Administration of iron isomaltoside led to significant increases in Hb. The effect on Hb was more pronounced in the patients who were anemic prior to treatment. Although the patients had significant increases in Hb and iron parameters, more than one in four patients were still anemic after one iron treatment	Ferritin and TSAT increased significantly. However, only 49% reached a ferritin level of 100 µg/L. The majority (95%) of patients received their prescribed dose of iron isomaltoside in one visit	ADRs were observed in 4% of the patients. In all cases, the patients fully recovered	29
Cancer-associated anemia								
Open-label, randomized, comparative, noninferiority trial	An adapted Ganzoni formula was used for calculating the iron need. Iron isomaltoside was administered as maximum 1,000 mg as single doses or bolus injections of 500 mg once weekly	Cancer patients: 1. Ferritin <800 µg/L 2. TSAT <50% 3. Not receiving ESA treatment	351	24 weeks	Iron isomaltoside was noninferior to iron sulfate in its ability to increase Hb from baseline to week 4 ($P=0.0002$). In addition, there was a faster onset of the Hb response in the IV iron isomaltoside infusion group compared to oral iron at week 1 ($P=0.03$) and a sustained effect on Hb in both groups until week 24	–	More patients experienced an ADR in the oral iron group (19 versus 7%; $P=0.0003$)	21

Cardiac surgery								
Double-blind, randomized, placebo-controlled, comparative trial	Iron isomaltoside was administered as a single infusion of 1,000 mg (maximum 20 mg/kg). 100 mL saline was used as placebo	Patients undergoing elective or subacute CABG, valve replacement: 1. Hb ≥12 g/dL for women and Hb ≥13 g/dL for men 2. Ferritin ≤800 µg/L	60	4 weeks	There was an expected decrease in Hb from baseline to week 4 in both treatment groups but it was significantly less pronounced in the iron isomaltoside group compared to the placebo group (P=0.0124)	Ferritin and TSAT increased significantly in the iron isomaltoside group when compared to the placebo group (P<0.01)	No ADRs or fatal events were observed	22
Chronic heart failure (CHF)								
Open-label, noncomparative, pilot trial	An adapted Ganzoni formula was used for calculating the iron need All patients received a high single full iron repletion dose	CHF patients: 1. Hb <11 g/dL 2. Ferritin <800 µg/L	20	8 weeks	Hb was increased at every visit compared with baseline; however, the increase was nonsignificant probably due to the small number of patients	Ferritin was significantly increased at all visits, while a statistical increase in iron and TSAT were observed 1 week after baseline. All QoL assessments showed a significant increase 4 weeks after baseline	No ADR was reported	17
Postpartum hemorrhage								
Open-label, randomized trial	The women were allocated to either a single dose of 1,200 mg of IV iron isomaltoside or standard medical care with oral iron	Women with postpartum hemorrhage exceeding 700 mL	200	12 weeks	There was a statistically significant increase in Hb in women treated with IV iron compared to those treated with oral iron (P<0.05)	Aggregated change in physical fatigue within 12 weeks postpartum showed a statistical difference in favor of iron isomaltoside. A transient raise in iron content in maternal milk was observed within the first week after treatment	No serious ADR or hypersensitivity reactions were reported	23, 31

Abbreviations: ADR, adverse drug reaction; AE, adverse event; CABG:, coronary artery bypass graft; CKD, chronic kidney disease; CHF, chronic heart failure; CRP, C-reactive protein; ESA, erythropoiesis-stimulating agent; Hb, hemoglobin; IBD, inflammatory bowel disease; IV, intravenous; NDD-CKD, nondialysis-dependent chronic kidney disease; QoL, quality of life; SD, standard deviation; TSAT, transferrin saturation; ULN, upper limit of normal.

was noninferior to iron sulfate in its ability to increase Hb from baseline to week 4 (P=0.0002). In addition, there was a faster onset of the Hb response in the IV iron isomaltoside infusion group compared to oral iron group at week 1 (P=0.03) and a sustained effect on Hb in both groups until week 24. The authors concluded that the trial demonstrated a comparable sustained increase in Hb over time with both iron isomaltoside and oral iron and that more adverse drug reactions were reported for oral iron.[21]

Iron isomaltoside administered to patients undergoing cardiac surgery

Johansson et al[22] compared iron isomaltoside to placebo in the ability to change Hb from baseline to 4 weeks in patients undergoing elective or subacute coronary artery bypass graft, valve replacement, or a combination thereof. There was an expected decrease in Hb from baseline to week 4 in both treatment groups, but it was significantly less pronounced in the iron isomaltoside group compared to the placebo group (P=0.012), and the proportion of nonanemic patients at week 4 was significantly higher in the iron isomaltoside group (38.5% versus 8%; $P<0.05$). The authors concluded that iron isomaltoside could be used safely and effectively to prevent anemia after cardiac surgery and that the hemopoietic response is already evident at day 5.[22]

Iron isomaltoside administered to patients with chronic heart failure

Hildebrandt et al[17] investigated the safety profile of a high, single dose of iron isomaltoside in a small group of patients with CHF, and secondary endpoints included effects on relevant hematology parameters and QoL (measured by Linear Analog Scale Assessment). No adverse drug reaction was reported and no acute or delayed hypersensitivity reactions were observed. There were no significant changes in routine clinical safety laboratory tests or vital signs.

Hb and iron parameters increased at every visit compared with baseline. All QoL assessments showed a significant increase 4 weeks after baseline. The authors concluded that, despite the uncontrolled trial design and small sample size, iron isomaltoside was well tolerated and improved QoL in patients with CHF.[17]

Iron isomaltoside administered to women with postpartum hemorrhage

Holm et al[30] published a protocol for a trial in women with postpartum hemorrhage, and the trial was later presented as two abstracts at the XXI FIGO world congress in October 2015.[23,31] The primary outcome was the aggregated change in physical fatigue within 12 weeks postpartum, which showed a statistical difference in favor of iron isomaltoside.[23] In addition, the iron content in maternal milk samples was assessed in 65 women (30 treated with IV iron and 35 with standard medical care).[31] Mean (± SD) iron content in maternal milk 3 days after intervention was 0.72±0.27 and 0.40±0.18 mg/L ($P<0.001$) in the two treatment arms, respectively. One week after intervention, the mean iron in maternal milk was 0.47±0.17 and 0.44±0.25 mg/L ($P>0.05$), respectively. These mean values were all within the normal reference range for iron content in breast milk. The authors concluded that high-dose iron isomaltoside was associated with less fatigue within 12 weeks after postpartum hemorrhage.[31]

Iron isomaltoside and toxicology

IV iron preparations can cause oxidative stress,[32] impaired immunoactivation,[9] and renal injury.[33]

Fell et al[9] investigated the in vitro effects of IV iron preparations on mature circulating monocytes and hematopoietic stem cells. The purpose of this study was to investigate the immunoactivation of different monocyte subsets by five different IV iron preparations that are commonly used in clinical nephrology: iron isomaltoside, iron sucrose, ferric carboxymaltose, low-molecular-weight iron dextran, and ferumoxytol. Both therapeutically recommended and supratherapeutic doses were tested. Iron sucrose induced significant deleterious changes in monocytic immune function, which occurred even at lower, therapeutically recommended dosages, whereas the other IV iron preparations had no relevant effects at any dosage. The clinical relevance of these findings requires further investigation, but the authors suggested that repetitive infusion of iron sucrose for treatment of anemia in CKD may be considered as potentially immunoactivating.[9]

It has been suggested that parenteral iron may have a direct toxic effect on renal tubular cells. Zager et al[33] compared the nephrotoxicity of iron sucrose, iron gluconate, iron dextran, and iron isomaltoside over a broad dosage range (control and range: 30–1,000 µg iron/mL). In vitro toxicity was assessed by reduction in tubule adenosine triphosphate dehydrogenase production as well as lethal cell injury (% lactate dehydrogenase release). Up to 30-fold differences in severity of toxicity were observed, the highest toxicity being with iron sucrose and the lowest with iron dextran and iron isomaltoside.[33] No clinically significant

toxicity relative to these findings has been demonstrated to date.

Iron isomaltoside and phosphate/fibroblast growth factor 23

Hypophosphatemia, especially when severe, can be associated with several complications.[34] IV iron complexes differ in their capability to induce unintended hypophosphatemia[35–42] to a degree defined as medically significant (ie, <2 mg/dL).[43]

The effect of iron isomaltoside on serum phosphate has been evaluated in several trials.[13,15,16,18–23] The frequency of hypophosphatemia in iron isomaltoside-treated patients is low (Table 2). This transient minor decrease in phosphate observed shortly after dosing seems to be a class effect as it has been recognized with a number of different IV irons, and may be related to phosphate uptake in maturing erythrocytes.

In contrast, some irons do cause hypophosphatemia more frequently or to more pronounced degrees. Van Wyck et al[41] reported that 70% of the patients had hypophosphatemia when treated with ferric carboxymaltose, and in a trial by Hardy and Vandemergel,[34] 13% of patients treated with this formulation developed severe and prolonged hypophosphatemia. The reported clinical consequences of more pronounced hypophosphatemia have ranged from short-term fatigue and general weakness to fractures.[44–46] The more pronounced hypophosphatemia seems to be mediated by fibroblast growth factor 23 (FGF23),[34] which is a phosphate-regulating peptide hormone secreted by osteocytes, previously reported to be involved in hypophosphatemia.[38,42,47–49] Although the mechanism is poorly understood, it has been suggested that the intact and biologically active FGF23 hormone leads to suppression of renal tubular phosphate reabsorption and 1α-hydroxylation of vitamin D, resulting in hypophosphatemia.[38] FGF23 has also been shown to be associated with atherosclerosis, left ventricular hypertrophy, and cancer progression.[50–53]

Wolf et al[42] found that IV iron lowers the C-terminal FGF23 in humans by reducing its transcription, whereas the carbohydrate moieties in certain iron preparations, such as ferric carboxymaltose, seem to inhibit FGF23 degradation in osteocytes, leading to transient increases in intact and biologically active FGF23 hormone and reduced phosphate levels. Thus, according to Wolf et al[42] the more pronounced hypophosphatemic effect of iron is not a class effect, and the mechanism is substance-specific. There is no evidence that an FGF23-related mechanism occurs with use of iron isomaltoside.

Table 2 Hypophosphatemia incidences in trials with iron isomaltoside

Indication	Frequency of hypophosphatemia (%)	Reference
Nephrology		
Chronic kidney disease	0	13
Chronic kidney disease	1.3	15
Nondialysis-dependent chronic kidney disease	1.8	16
Inflammatory bowel	7	18
disease	0	19
Cardiology	0	22
Women with postpartum hemorrhage	5	23

Pharmacoeconomics of iron isomaltoside

If the full iron replacement dose is administered at a single visit then it would offer optimal convenience and improve overall pharmacoeconomics for both patient (less disruption of life, less time away from home/work, reduced injection numbers, lower exposure to the potential of side effects) and the hospital/health service (reduced number of visits, reduced physician and nurse time, improved outpatient management, improved cost-effectiveness).[54,55] This is supported by the new NICE guideline from 2015, which recommends consideration of high-dose, low-frequency IV iron as the treatment of choice for adults and young people with IDA not receiving hemodialysis.[56] Furthermore, the guideline ranks iron isomaltoside as the most cost-effective IV iron for nondialysis patients.[56] In a recent trial, infusions of iron isomaltoside administered as single doses up to 1,500 mg, and cumulative doses up to 3,000 mg over a short time period, were completed without safety concerns representing promising treatment alternatives to current practice.[20]

A cost analysis of the two main "modern" irons, iron isomaltoside and ferric carboxymaltose, compared to standard treatments (blood transfusion, iron sucrose, and low-molecular-weight iron dextran) considered the cost of the treatment including nursing costs associated with administration, equipment for administration, and patient transportation.[57,58] Iron isomaltoside provided a net saving when compared with blood transfusion, iron sucrose, and ferric carboxymaltose. At two dose levels (600 and 1,000 mg), iron isomaltoside was also less expensive than low-molecular-weight iron dextran, but it was more expensive at a dose of 1,600 mg. However, low-molecular-weight iron

dextran is administered over a longer time period, which is inconvenient for the patient and consumes more health-care resource.[57,58] These data indicate that iron isomaltoside can be cost beneficial compared with other parenteral iron products, at least from these previous cost analyses.

Conclusion

New IV iron preparations should ideally be capable of delivering a wide dosing range to allow iron correction in a single or low number of visits, a rapid infusion, and minimal potential side effects including low catalytic/labile iron release, and minimal risk of anaphylaxis. Furthermore, they should be convenient for the patient and the health-care professional, and cost effective for the health-care system. The intention behind the development of iron isomaltoside was to fulfill these requirements. Iron isomaltoside has been shown to be effective in treating IDA across multiple therapeutic patient groups and compared to placebo, IV iron sucrose, and oral iron. It has a low immunogenic potential, a low potential to release labile iron, and does not appear to be associated with clinically significant hypophosphatemia.

The frequency of observed serious hypersensitivity reactions in clinical trials with iron isomaltoside is very low. Milder infusion-related reactions may occur and are often misinterpreted and misclassified. Longer-term safety data are not available at present.

The very rare serious hypersensitivity reactions that are potentially life-threatening, according to the European Medicines Agency, may be seen with all iron preparations. An algorithm outlining grading and management of acute hypersensitivity reactions to IV iron infusions can be found in the review by Rampton et al[59] and is very helpful in clinical practice.

However, there is logic in reducing exposure of IDA patients to this risk by providing full iron repletion in the minimum number of administrations, and iron isomaltoside can fulfill this desire. In conclusion, the currently available and reviewed trials indicate that iron isomaltoside has demonstrated robust efficacy and a good safety profile in CKD and across other therapeutic groups suffering from ID or IDA.

Acknowledgments

The authors gratefully acknowledge the medical writing assistance provided by Eva-Maria Damsgaard Nielsen. Eva-Maria Damsgaard Nielsen is employed by Pharmacosmos A/S.

Disclosure

Philip A Kalra has received honoraria for lectures and advisory board participation from Pharmacosmos A/S, Vifor, and Takeda. Sunil Bhandari received speaker and consultancy fees from Pharmacosmos A/S. The authors report no other conflicts of interest in this work.

References

1. Mehdi U, Toto RD. Anemia, diabetes, and chronic kidney disease. *Diabetes Care*. 2009;32(7):1320–1326.
2. Groopman JE, Itri LM. Chemotherapy-induced anemia in adults: incidence and treatment. *J Natl Cancer Inst*. 1999;91(19):1616–1634.
3. Steinmetz HT. The role of intravenous iron in the treatment of anemia in cancer patients. *Ther Adv Hematol*. 2012;3(3):177–191.
4. Dignass AU, Gasche C, Bettenworth D, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. *J Crohns Colitis*. 2015;9(3):211–222.
5. Henry DH. The role of intravenous iron in cancer-related anemia. *Oncology (Williston Park)*. 2006;20(8 Suppl 6):21–24.
6. KDIGO. KDIGO clinical practice guideline for anemia in chronic kidney disease. *Kidney Int*. 2012;2(4). Available from: http://kdigo.org/home/guidelines/anemia-in-ckd/. Accessed November 13, 2015.
7. Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. *Inflamm Bowel Dis*. 2007;13(12):1545–1553.
8. Jahn MR, Andreasen HB, Futterer S, 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(3):480–491.
9. Fell LH, Zawada AM, Rogacev KS, Seiler S, Fliser D, Heine GH. Distinct immunologic effects of different intravenous iron preparations on monocytes. *Nephrol Dial Transplant*. 2014;29(4):809–822.
10. Fell LH, Zawada AM, Seiler S, Untersteller K, Fliser D, Heine GH. Impact of individual IV iron preparations on differentiation of macrophages and dendritic cells [poster FO014]. Poster presented at: 52nd Congress of ERA-EDTA, May 28–31, 2015, London, UK.
11. Iron Isomaltoside 1000 (Monofer®) [summary of product characteristics]. Holbaek, Denmark: Pharmacosmos A/S; 2014.
12. Nordfjeld K, Andreasen H, Thomsen LL. Pharmacokinetics of iron isomaltoside 1000 in patients with inflammatory bowel disease. *Drug Des Devel Ther*. 2012;6:43–51.
13. Gupta DR, Larson DS, Thomsen LL, Coyne DW. Pharmacokinetics of iron isomaltoside 1000 in patients with stage 5 chronic kidney disease on dialysis therapy. *J Drug Metab Toxicol*. 2013;4:152.
14. Wikström B, Bhandari S, Barany P, et al. Iron isomaltoside 1000: a new intravenous iron for treating iron deficiency in chronic kidney disease. *J Nephrol*. 2011;24(5):589–596.
15. Bhandari S, Kalra PA, Kothari J, et al. A randomized, open-label trial of iron isomaltoside 1000 (Monofer®) compared with iron sucrose (Venofer®) as maintenance therapy in haemodialysis patients. *Nephrol Dial Transplant*. 2015;30(9):1577–1589.
16. Kalra PA, Bhandari S, Saxena S, et al. A randomized trial of iron isomaltoside 1000 versus oral iron in non-dialysis-dependent chronic kidney disease patients with anaemia. *Nephrol Dial Transplant*. 2015. Epub August 6, 2015.
17. Hildebrandt PR, Bruun NE, Nielsen OW, et al. Effects of administration of iron isomaltoside 1000 in patients with chronic heart failure. A pilot study. *Transfus Altern Transfus Med*. 2010;11(4):131–137.
18. Reinisch W, Staun M, Tandon RK, et al. A randomized, open-label, non-inferiority study of intravenous iron isomaltoside 1,000 (Monofer) compared with oral iron for treatment of anemia in IBD (PROCEED). *Am J Gastroenterol*. 2013;108(12):1877–1888.
19. Reinisch W, Altorjay I, Zsigmond F, et al. A 1-year trial of repeated high-dose intravenous iron isomaltoside 1000 to maintain stable hemoglobin levels in inflammatory bowel disease. *Scand J Gastroenterol*. 2015;50(10):1226–1233.
20. Dahlerup J, Lindgren S. High dose intravenous iron isomaltoside 1000 in patients with inflammatory bowel disease – the PROMISE trial. Poster presenter at: 10th Congress of the European Crohn's and Colitis Organisation (ECCO), February 18–21, 2015, Barcelona, Spain.

21. Birgegård G, Henry D, Thomsen LL, Auerbach M. Intravenous iron isomaltoside 1000 (Monofer®) as mono therapy in comparison with oral iron sulphate in patients with non-myeloid malignancies associated with chemotherapy induced anaemia (CIA). Abstract presented at: The MASCC/ISOO Annual Meeting on Supportive Care in Cancer, June 25–27, 2015, Copenhagen, Denmark.
22. Johansson PI, Rasmussen AS, Thomsen LL. Intravenous iron isomaltoside 1000 (Monofer®) reduces postoperative anaemia in preoperatively non-anaemic patients undergoing elective or subacute coronary artery bypass graft, valve replacement or a combination thereof: a randomized double-blind placebo-controlled clinical trial (the PROTECT trial). *Vox Sang*. 2015;109(3):257–266.
23. Holm C, Thomsen LL, Norgaard A, Langhoff-Roos J. Intravenous iron isomaltoside 1000 (Monofer) administered by a high single dose infusion or standard medical care for the treatemt of fatigue in women after postpartum haemorrhage: a rondomized controlled trial. *Int J Gynecol Obstet*. 2015;131(Suppl 5):E118.
24. Wikstrom B, Bhandari S, Barany P, Kalra PA, Ladefoged S, Wilske J. Monofer, a novel intravenous iron oligosaccharide for treatment of iron deficiency in patients with chronic kidney disease (CKD) [poster M560]. Poster presented at: World Congress of Nephrology, May 22–26, 2009, Milan, Italy.
25. Leistikow F, Walper A, Ammer R, Hellmann B. Prospective observational study of the efficacy, safety and tolerability of iron isomaltoside 1000 in the treatment of iron deficiency anemia in patients with chronic renal failure. *Nephrol Dial Transplant*. 2015;30(Suppl 3):iii201–iii202.
26. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol*. 2008;103(5):1182–1192.
27. Evstatiev R, Marteau P, Iqbal T, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. *Gastroenterology*. 2011;141(3):846–853.
28. Gozzard D. When is high-dose intravenous iron repletion needed? Assessing new treatment options. *Drug Des Devel Ther*. 2011; 5:51–60.
29. Frigstad SO, Rannem T, Hellstrom PM, Hammarlund P, Bonderup O. A Scandinavian prospective observational study of iron isomaltoside 1000 treatment: clinical practice and outcomes in iron deficiency anaemia in patients with IBD [poster P481]. Poster presented at: 10th Congress of the European Crohn's and Colitis Organisation (ECCO), February 8–21, 2015, Barcelona, Spain.
30. Holm C, Thomsen LL, Norgaard A, Langhoff-Roos J. Intravenous iron isomaltoside 1000 administered by high single-dose infusions or standard medical care for the treatment of fatigue in women after postpartum haemorrhage: study protocol for a randomised controlled trial. *Trials*. 2015;16:5.
31. Holm C, Thomsen LL, Norgaard A, Langhoff-Roos J. Iron content in breast milk from mothers treated with a high single dose infusion of iron isomaltoside 1000 (Monofer). *Int J Gynecol Obstet*. 2015; 131(Suppl 5):E119.
32. Agarwal R, Vasavada N, Sachs NG, Chase S. Oxidative stress and renal injury with intravenous iron in patients with chronic kidney disease. *Kidney Int*. 2004;65(6):2279–2289.
33. Zager RA, Johnson AC, Hanson SY. Parenteral iron nephrotoxicity: potential mechanisms and consequences. *Kidney Int*. 2004;66(1): 144–156.
34. Hardy S, Vandemergel X. Intravenous iron administration and hypophosphatemia in clinical practice. *Int J Rheumatol*. 2015;2015: 468675.
35. FDA Advisory Committee Briefing Document, Drug Safety and Risk Management Committee. Division of Medical Imaging and Hematology Products and Office of Oncology Drug Products and Office of New Drugs, New Drug Application (NDA) 22-054 for Injectafer (Ferric Carboxymaltose) for the treatment of iron deficiency anemia in patients with heavy uterine bleeding or postpartum patients. February 1, 2008. Available from: http://www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4337b1-01-fda.pdf. Accessed November 13, 2015.
36. Sato K, Nohtomi K, Demura H, et al. Saccharated ferric oxide (SFO)-induced osteomalacia: in vitro inhibition by SFO of bone formation and 1,25-dihydroxy-vitamin D production in renal tubules. *Bone*. 1997;21(1):57–64.
37. Sato K, Shiraki M. Saccharated ferric oxide-induced osteomalacia in Japan: iron-induced osteopathy due to nephropathy. *Endocr J*. 1998;45(4):431–439.
38. Schouten BJ, Hunt PJ, Livesey JH, Frampton CM, Soule SG. FGF23 elevation and hypophosphatemia after intravenous iron polymaltose: a prospective study. *J Clin Endocrinol Metab*. 2009;94(7): 2332–2337.
39. Schouten BJ, Doogue MP, Soule SG, Hunt PJ. Iron polymaltose-induced FGF23 elevation complicated by hypophosphataemic osteomalacia. *Ann Clin Biochem*. 2009;46(Pt 2):167–169.
40. Okada M, Imamura K, Iida M, Fuchigami T, Omae T. Hypophosphatemia induced by intravenous administration of Saccharated iron oxide. *Klin Wochenschr*. 1983;61(2):99–102.
41. Van Wyck DB, Mangione A, Morrison J, Hadley PE, Jehle JA, Goodnough LT. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. *Transfusion*. 2009;49(12):2719–2728.
42. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. *J Bone Miner Res*. 2013;28(8):1793–1803.
43. U.S. Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events (CTCAE), Version 4.02 28 May 2009. Available from: http://evs.nci.nih.gov/ftp1/CTCAE/Archive/CTCAE_4.02_2009-09-15_QuickReference_8.5x11.pdf. Accessed November 13, 2015.
44. Blazevic A, Hunze J, Boots JM. Severe hypophosphataemia after intravenous iron administration. *Neth J Med*. 2014;72(1):49–53.
45. Vandemergel X, Vandergheynst F. Potentially life-threatening phosphate diabetes induced by ferric carboxymaltose injection: a case report and review of the literature. *Case Rep Endocrinol*. 2014;2014:843689.
46. Moore KL, Kildahl-Andersen O, Kildahl-Andersen R, Tjonnfjord GE. Uncommon adverse effect of a common medication. *Tidsskr Nor Laegeforen*. 2013;133(2):165.
47. Durham BH, Joseph F, Bailey LM, Fraser WD. The association of circulating ferritin with serum concentrations of fibroblast growth factor-23 measured by three commercial assays. *Ann Clin Biochem*. 2007; 44(Pt 5):463–466.
48. Imel EA, Peacock M, Gray AK, Padgett LR, Hui SL, Econs MJ. Iron modifies plasma FGF23 differently in autosomal dominant hypophosphatemic rickets and healthy humans. *J Clin Endocrinol Metab*. 2011;96(11):3541–3549.
49. Shimizu Y, Tada Y, Yamauchi M, et al. Hypophosphatemia induced by intravenous administration of saccharated ferric oxide: another form of FGF23-related hypophosphatemia. *Bone*. 2009;45(4):814–816.
50. Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest*. 2011;121(11):4393–4408.
51. Feng S, Wang J, Zhang Y, Creighton CJ, Ittmann M. FGF23 promotes prostate cancer progression. *Oncotarget*. 2015;6(19):17291–17301.
52. Biscetti F, Straface G, Porreca CF, et al. Increased FGF23 serum level is associated with unstable carotid plaque in type 2 diabetic subjects with internal carotid stenosis. *Cardiovasc Diabetol*. 2015;14(1):139.
53. Mirza MA, Larsson A, Lind L, Larsson TE. Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community. *Atherosclerosis*. 2009;205(2):385–390.
54. Cancado RD, Munoz M. Intravenous iron therapy: how far have we come? *Rev Bras Hematol Hemoter*. 2011;33(6):461–469.
55. Bhandari S, Naudeer S. Improving efficiency and value in health care. Intravenous iron management for anaemia associated with chronic kidney disease: linking treatment to an outpatient clinic, optimizing service provision and patient choice. *J Eval Clin Pract*. 2008;14(6):996–1001.
56. NICE Guideline NG8. Chronic kidney disease: managing anemia. June 3, 2015. Available from: https://www.nice.org.uk/guidance/ng8. Accessed November 13, 2015.

57. Bhandari S. A hospital-based cost minimization study of the potential financial impact on the UK health care system of introduction of iron isomaltoside 1000. *Ther Clin Risk Manag*. 2011;7:103–113.
58. Bhandari S. Update of a comparative analysis of cost minimization following the introduction of newly available intravenous iron therapies in hospital practice. *Ther Clin Risk Manag*. 2011;7:501–509.
59. Rampton D, Folkersen J, Fishbane S, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. *Haematologica*. 2014;99(11):1671–1676.