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

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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.3,6,7
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. 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.

In the European Union, iron isomaltoside can be administered with a maximum single dosage of 20 mg/kg actual body weight. 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. 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 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 (Cmax), with no difference in elimination rate constant (K) and half-life (T1/2) between the 100, 200, and 500 mg IV bolus doses of iron isomaltoside. The T1/2 was between 28.86 and 31.14 hours, and time to reach maximum concentration (Tmax) was between 0.57 and 1 hour.

A second open-label, single-center, crossover PK trial was performed in 12 patients (five men, seven women) with inflammatory bowel disease (IBD). 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.

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, those with nondialysis-dependent chronic kidney disease (NDD-CKD), those with chronic heart failure (CHF), IBD, and underlying cancer, those undergoing cardiac surgery, and women with postpartum hemorrhage. 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 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
Iron isomaltoside administered to patients with IDA

The potential for iron isomaltoside treatment to improve iron status and anemia was first evaluated by Kalra et al.,

where patients with IDA were randomly assigned to either treatment with oral iron sulfate or IV iron isomaltoside over a 12-week period. The primary outcome was the increase in Hb concentration from baseline to week 4. The results showed that iron isomaltoside resulted in a significantly higher increase in Hb than oral iron sulfate (mean increase: 2.58 vs 1.18 g/dL, P=0.002). In addition, iron isomaltoside was more efficacious in maintaining Hb concentrations in patients with IDA than oral iron sulfate, with a response rate of 74% (74/100) for iron isomaltoside versus 60% (60/100) for oral iron sulfate (P=0.039; per protocol: P=0.047).

Frigstad et al.,

presented an observational study in which patients were treated with iron isomaltoside (mean dose: 1,800 mg) and cumulative doses of up to 3,000 mg over a short duration. They found that iron isomaltoside could avoid episodes of IDA without major safety issues.

In 2015, Bhandari et al. demonstrated that iron isomaltoside is efficacious in increasing Hb levels in patients with IBD. The study was a label, multicenter trial conducted in 21 patients with IBD and patients with IDA. The authors concluded that repeated treatment of iron deficiency (ID) with iron isomaltoside could avoid episodes of IDA without major safety issues.

Iron isomaltoside administered to patients with anemia

Birgegård et al. 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 the ability to increase Hb at week 8 in patients with 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.

Thus, the authors suggested that the cumulative IV dosing may have been too low in this trial, which harmonizes with Gozzard’s 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. reported a 1-year extension trial of this IBD trial evaluating the need for additional IV iron isomaltoside doses to maintain a stable Hb. 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.

Dahlerup and Lindgren presented a prospective, open-label, multicenter trial conducted in 21 patients with IBD and patients with 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.
<table>
<thead>
<tr>
<th>Trial design</th>
<th>Dosing regimen</th>
<th>Main inclusion criteria</th>
<th>Number of patients</th>
<th>Duration</th>
<th>Main efficacy results</th>
<th>Other findings</th>
<th>Main safety results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Chronic kidney disease (CKD); dialysis and nondialysis</strong></td>
<td>Open-label, noncomparative trial</td>
<td>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</td>
<td>182</td>
<td>8 weeks</td>
<td>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 &lt; 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)</td>
<td>TSAT and ferritin increased significantly from baseline to week 8 (P &lt; 0.001)</td>
<td>Nineteen ADRs were reported of which two were serious. The two serious ADRs were sepsis with <em>Staphylococcus aureus</em> and unstable angina, neither of which were directly attributed to iron administration. No acute hypersensitivity reaction or delayed allergic reactions were reported</td>
<td>14</td>
</tr>
<tr>
<td><strong>Observational study</strong></td>
<td>Iron isomaltoside was administered according to usual daily clinical practice and in accordance with the authorized indication</td>
<td>Dialysis and NDD-CKD patients with CKD stage 3–5</td>
<td>695</td>
<td>9 months</td>
<td>Mean (SD) Hb increased from 11.0 (1.7) to 11.6 (1.6) g/dL (P = 0.0001)</td>
<td>Ferritin and TSAT increased significantly (P &lt; 0.0001). The proportion of patients treated with ESA decreased significantly when the patients received iron isomaltoside (P &lt; 0.002)</td>
<td>No ADR was reported</td>
<td>25</td>
</tr>
<tr>
<td><strong>Chronic kidney disease; nondialysis</strong></td>
<td>Open-label, randomized, comparative, noninferiority trial</td>
<td>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</td>
<td>351</td>
<td>8 weeks</td>
<td>Iron isomaltoside was noninferior to iron sulfate in its ability to increase Hb from baseline to week 4 (P &lt; 0.001). In addition, iron isomaltoside also showed superiority over oral iron (P = 0.05)</td>
<td>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 &lt; 0.01)</td>
<td>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)</td>
<td>16</td>
</tr>
</tbody>
</table>
Iron isomaltoside – efficacy and safety

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: 351
1. Hb between 9.5 and 12.5 g/dL
2. Ferritin < 800 μg/L
3. TSAT < 35%
4. Stable ESA treatment
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%], one staphylococcal bacteremia and one event of dyspnea [treated as a hypersensitivity reaction] in the iron sucrose group [2/114, 1.8%])

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: 338
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%
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 ≥2 g/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

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: 39
1. Who completed the lead-in trial or
2. Discontinued from the lead-in trial due to intolerance to oral iron
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

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<table>
<thead>
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</tr>
</thead>
<tbody>
<tr>
<td>Open-label safety trial</td>
<td>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</td>
<td>IBD patients: 1. Hb &lt;12 g/dL for women and Hb &lt;13 g/dL for men 2. Patients with CRP above the ULN of normal had to have a ferritin &lt;100 μg/L; patients with a CRP ≥ ULN had to have a ferritin &lt;30 μg/L</td>
<td>21</td>
<td>8 or 16 weeks</td>
<td>There was a significant increase in Hb at all time points within both treatment groups (P&lt;0.05)</td>
<td>There was a significant increase in TSAT at all time points within both treatment groups (P&lt;0.05)</td>
<td>Four patients experienced nine ADRs. In all cases, the patients fully recovered</td>
<td>20</td>
</tr>
<tr>
<td>Observational study</td>
<td>Iron isomaltoside was administered according to two different calculations: 1. simplified dosing approach or 2. Ganzoni formula</td>
<td>IBD patients</td>
<td>149</td>
<td>–</td>
<td>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</td>
<td>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</td>
<td>ADRs were observed in 4% of the patients. In all cases, the patients fully recovered</td>
<td>29</td>
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<td>Cancer-associated anemia</td>
<td>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</td>
<td>Cancer patients: 1. Ferritin &lt;800 μg/L 2. TSAT &lt;50% 3. Not receiving ESA treatment</td>
<td>351</td>
<td>24 weeks</td>
<td>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</td>
<td>–</td>
<td>More patients experienced an ADR in the oral iron group (19 versus 7%; P=0.0003)</td>
<td>21</td>
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Cardiac surgery
Iron isomaltoside was administered as a single infusion of 1,000 mg (maximum 20 mg/kg) to 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. 100 mL saline was used as placebo.

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.

Chronic heart failure (CHF)
An adapted Gaszoni formula was used for calculating the iron need. All patients received a high single full iron repletion dose.

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.

Postpartum hemorrhage
Women with postpartum hemorrhage exceeding 700 mL were allocated to either a single dose of 1,200 mg of IV iron isomaltoside or standard medical care with oral iron.

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.

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, non-dialysis-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.\textsuperscript{21}

**Iron isomaltoside administered to patients undergoing cardiac surgery**

Johansson et al\textsuperscript{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.\textsuperscript{22}

**Iron isomaltoside administered to patients with chronic heart failure**

Hildebrandt et al\textsuperscript{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.\textsuperscript{17}

**Iron isomaltoside administered to women with postpartum hemorrhage**

Holm et al\textsuperscript{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.\textsuperscript{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.\textsuperscript{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).\textsuperscript{31} Mean ($\pm$ SD) iron content in maternal milk 3 days after intervention was 0.72$\pm$0.27 and 0.40$\pm$0.18 mg/L ($P<0.001$) in the two treatment arms, respectively. One week after intervention, the mean iron in maternal milk was 0.47$\pm$0.17 and 0.44$\pm$0.25 mg/L ($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.\textsuperscript{31}

**Iron isomaltoside and toxicology**

IV iron preparations can cause oxidative stress,\textsuperscript{32} impaired immunoactivation,\textsuperscript{9} and renal injury.\textsuperscript{13}

Fell et al\textsuperscript{8} 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 monocyctic 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.\textsuperscript{8}

It has been suggested that parenteral iron may have a direct toxic effect on renal tubular cells. Zager et al\textsuperscript{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.\textsuperscript{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. IV iron complexes differ in their capability to induce unintended hypophosphatemia to a degree defined as medically significant (ie, <2 mg/dL). 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 reported that 70% of the patients had hypophosphatemia when treated with ferric carboxymaltose, and in a trial by Hardy and Vandemergel, 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. The more pronounced hypophosphatemia seems to be mediated by fibroblast growth factor 23 (FGF23), which is a phosphate-regulating peptide hormone secreted by osteocytes, previously reported to be involved in hypophosphatemia. 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. FGF23 has also been shown to be associated with atherosclerosis, left ventricular hypertrophy, and cancer progression.

Wolf et al 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, 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.

**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). 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. Furthermore, the guideline ranks iron isomaltoside as the most cost-effective IV iron for nondialysis patients. 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.

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. 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

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**Table 2** Hypophosphatemia incidences in trials with iron isomaltoside

<table>
<thead>
<tr>
<th>Indication</th>
<th>Frequency of hypophosphatemia (mg)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nephrology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>1.3</td>
<td>15</td>
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<td>Nondialysis-dependent</td>
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<tr>
<td>chronic kidney disease</td>
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<td>Women with postpartum</td>
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<tr>
<td>hemorrhage</td>
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</table>
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 al59 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.

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