According to the WHO guidelines anemia is a hemoglobin (HGB) concentration < 13 g/dL for men, < 12 g/dL for women who are not pregnant, < 11 g/dL for pregnant women, < 11 g/dL for children in the age of 0.5-5 years, < 11.5 g/dL for children in the age of 5-12 years and < 12 g/dL for children in the age of 12-15 years. It affects approximately 1.6 billion people worldwide, which is nearly 25% of the human population, and the main reason responsible for more than 50% of its cases is iron deficiency (1).

The total iron content in the body is approximately 3 g. Some of the indicators of its deficiency are: decreased volume of red blood cells (MCV – mean cell volume), low transferrin saturation (TSAT – transferrin saturation), lower iron concentration in plasma, increased iron binding capacity (TIBC – total iron binding capacity, UIBC - unsaturated iron binding capacity) and lower ferritin concentration. Loss of blood is one of the causes of iron-deficiency anemia (IDA) (for women in reproductive age it is related to menstrual bleedings, for other people mostly to the gastrointestinal tract), insufficient iron intake, deficient absorption form the gastrointestinal tract and states of increased demand. These factors can occur on their own or in any combination (2).

The protein ferroportin is responsible for the transmembrane iron transport from the enterocytes and the reticulo-endothelial system cells to blood. In case of a concomitant infection, liver cells increase production of hepcidin, a peptide hormone which is a ferroportin inhibitor, causing a decreased availability of iron for the erythropoiesis and leading to anemia of chronic diseases (3).

Replenishing an existing iron deficiency leads to normalization of HGB concentration within 4-6 weeks, without the risk of an excessive HGB increase, however the optimal route of iron administration remains under discussion (4). Oral iron formulations are a treatment of choice due to safety, low cost and easy administration. Unfortunately, this treatment is often insufficient, due to bad absorption and adverse reactions (ARs), mostly from the gastrointestinal tract. Approximately 56% of patients experience nausea, vomiting, diarrhoea, abdominal pain or constipation, that leads to discontinuation of treatment by 20% of patients (2).

Keywords: iron deficiency anemia, intravenous iron preparations, chronic kidney disease, heart failure, cancer

SAFETY AND EFFICACY OF INTRAVENOUS ADMINISTRATION OF IRON PREPARATIONS

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Abstract: Iron deficiency is the main cause of anemia worldwide. Iron supplementation leads to a rise of transferrin saturation and ferritin concentration, resulting in an increased hemoglobin level and decrease of anemia symptoms. Oral iron administration is a treatment of choice in iron deficiency anemia. In patients with impaired iron absorption from the gastrointestinal tract, as well as in large deficits, or poor tolerance of oral formulations, it becomes necessary to apply iron intravenously. In this paper we present, on the basis of current publications, the characteristics of intravenous iron preparations nowadays available on the market, in various clinical situations, with particular focus on their benefits and risk related to the administration of high single iron doses.

Keywords: iron deficiency anemia, intravenous iron preparations, chronic kidney disease, heart failure, cancer

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Intravenous (i.v.) iron preparations lead to a faster HGB increase and more efficient replenishment of iron storage in the body, with an acceptable safety profile. This is particularly important when occurs high demand for iron as in chronic kidney disease (CKD), blood loss caused by inflammatory gastrointestinal tract diseases (IBD - inflammatory bowel disease), or in other gastrointestinal pathologies, heavy uterine bleeding, pregnancy, blood loss during surgical procedures, chronic heart failure and anemia related to a cancer and its treatment (5, 6).

The total iron dose necessary to achieve a normal HGB concentration and replenish iron stores is calculated using the Ganzoni formula:

\[
\text{Total iron deficit [mg]} = \text{body weight (BW) [kg]} \times \left(\frac{\text{target HGB} - \text{actual HGB}}{\text{g/dL}}\right) \times 2.4 + \text{iron storage [mg]}. \]

Target HGB concentration in patients with a BW < 35 kg is 13 g/dL, and in patients with BW ≥ 35 kg - 15 g/dL. Iron supply pool for patients with BW < 35 kg is 15 mg/kg BW, and for patients with BW ≥ 35 kg - 500 mg. In case of patients with BW ≤ 66 kg, the calculated total iron dose needs to be rounded down to a full 100 mg, in case of patients with BW > 66 kg – it has to be rounded up to a full 100 mg (7).

Based on current publications, in this paper we will present the characteristics of iron preparations nowadays available on the market, destined for i.v. administration in the context of different clinical situations, with detailed analysis of risks and benefits of the i.v. use of a single high dose of iron.

**INTRA VENOUS IRON PREPARATIONS**

Globally, 7 iron preparation for i.v. administration are being used: high molecular weight iron dextran (HMWID), low molecular weight iron dextran (LMWID), iron gluconate (IG), iron sucrose (IS), iron ferrumoxytol (FO), ferric carboxymaltose (FCM) and ferric isomaltoside 1000 (FI). The latter three are new generation products with pharmacokinetic parameters allowing for a single high dose iron administration, without the need for a test dose. Only the latter two are authorized in Poland. Their efficacy in iron replenishment is similar, but they differ in size of a single dose, administration frequency, safety profile, availability on the market, as well as price (6).

High molecular weight iron dextran (HMWID; Dexferrum) is related to a higher risk of anaphylactic reactions and is not available in Europe (6). According to the data of the Food and Drug Administration (FDA) from 2001-2003, the number of reports of a life threatening adverse reaction for a million of applications of the products IS, IG, LMWID and HMWID has been 0.6, 0.9, 3.3, 11.3, respectively, for these reasons HMWID is no longer being used (7). These results do not necessarily reflect the actual state, as is being stressed also by the FDA, as the methodology of assessing the medicine product safety profile has not been appropriate and there is no certainty that the reported reactions have been in fact caused by the suspected product (4,8). On the other hand, an increased risk of hypersensitivity-related reactions after products containing dextran shell is confirmed by a comparison study of iron dextran and FCM (9).

Low molecular weight iron dextran (LMWID; CosmoFer, INFeD) compared to HMWID, is characterized by a better safety profile and allows for iron restoration with a single dose. However, it requires a test dose, and the infusion takes 4-6 h, depending on the iron dose (6).

Iron gluconate (IG; Ferrlecit) can be administered in a maximum dose of only 125 mg (10).

Iron sucrose (IS; Venofer) can be administered in a maximum single dose of 200 mg, which often requires repeated administration to replenish a significant iron deficiency. In Europe, a test dose is required before infusion (10). In many clinical studies it is being compared to oral and i.v. iron preparations.

Iron ferrumoxytol (FO; FeraHeme/Rienso) is in use since 2009, mostly in the USA in patients with chronic kidney disease (CKD) and iron deficiency. Lately, it has also been introduced to the European market, but it is still unavailable in Poland (11).

Ferric carboxymaltose (FCM; Ferinject, Injectafer) can supply 15 mg of iron/kg BW, maximum 1000 mg of iron in a single, 15 min i.v. administration (5). Depending on the dose, this causes a temporary increase of iron concentration in serum, ferritin concentration and transferrin saturation. FCM is quickly absorbed from peripheral blood and stored in bone marrow (approx. 80%), liver and spleen, where iron is being released for heme production (12). FCM was authorized in Europe in 2007. Due to a disproportionate number of deaths, reported after the assessment of 14 controlled and uncontrolled studies (FCM 14/2080, IS 1/145, products for oral administration 0/834), the FDA initially refused the authorization of FCM in the USA (13). However, after a longer observation of the product, it has been deemed safe and authorized for use in 2013 (11).

The results of few randomized studies, lasting for 6-12 weeks, comparing FCM (in majority the iron dose was ≤ 1000 mg or 15 mg/kg in patients
with BW < 66 kg, potential additional doses were being administered within one week intervals) to orally administered preparations (ferrous sulfate - FS), in daily doses of 3 × 65 mg or 2 × 100 mg) confirm that FCM is no less effective in increasing the HGB concentration and replenishment of iron supply in patients with IBD, heavy uterine bleeding, postpartum anemia and CKD (12). The HGB increase was faster after the administration of FCM than after the administration of FS. FCM has been well tolerated, most AR were mild or moderate in intensity (mostly headache, nausea, abdominal pain, constipation, diarrhea, rash and injection site reactions). The frequency of reported AR was similar in both groups (FCM vs. FS). Patients who received FCM had more often lowered phosphate concentration in blood serum, and compared to the FS group, they more often had a rash and injection site reactions, however gastrointestinal problems were more frequent in patients who were taking FS orally. In patients with heart failure and iron deficiency, FCM reduced symptoms, improved functionality and quality of life. This result was also observed in patients who didn’t initially suffer from anemia (HGB > 12 g/dL) (12).

Ferric isomaltoside 1000 (FI; Monofer / Monover, Diafer) has been used in Europe since 2009. It is a new non-dextran formulation for i.v. administration, strongly binding iron molecules, which allows for a controlled, slow release of iron binding proteins, preventing its toxicity. Additionally, the linear structure of the carbohydrate part of the isomaltoside 1000 results in lower immunogenicity of the product, which means that no test dose is required before infusion.

An in vitro study comparing the impact of three different concentrations of IS, FCM, FI, LMWID, and FO preparations on monocytes, has showed that only IS impaired monocyte function in vitro, which can lead to an attenuation of the immune system and increase the possibility of infection, however, the clinical impact of this phenomenon requires further analysis (14).

The British study compared the cost of purchase and administration of iron preparations in high doses (LMWID, FCM and FI in doses of 600, 1000 and 1600 mg) compared to traditional iron deficiency anemia treatment (blood products and IS). The comparison study of the cost related to drug purchase, medical care, used equipment and transportation cost, has showed that application of IS and blood transfusion were more cost generating, compared to other products. LMWID in a dose of 1600 mg is the cheapest product, but the infusion is time-consuming and a test dose before administration is required. In case of doses of 600 and 1000 mg, FI as well as FCM are more cost-effective than LMWID.

In scope of all studied doses, FI is less expensive, compared to FCM.

In summary, the new iron preparations seem to be a promising and cost-effective treatment options. However, in other countries pharmacoeconomic analysis can lead to different conclusions, due to different cost of medical care, equipment, transportation or price of a medicinal product (15). Table 1 presents characteristics of i.v. iron preparations (10, 16).

**DISEASES REQUIRING INTRAVENOUS IRON ADMINISTRATION**

**Chronic kidney disease (CKD)**

Iron deficiency occurs more often in people with CKD than in the general population, due to impaired absorption, lower intake caused by dietary restrictions, or lack of appetite, used medicines (proton-pump inhibitors, gastrointestinal phosphate binding preparations), chronic infections, and vitamin deficiencies. In more advanced stages of CKD, patients are subjected to frequent blood collecting and experience gastrointestinal bleeding as well. Annual iron loss for hemodialysis (HD) patients is 1-3 g due to repeated injections and blood loss in the dialyzer and blood lines, which is the equivalent of an annual blood loss of 2.5 L (17, 18). Simultaneously, the use of erythropoiesis-stimulating agent (ESA) increases iron demand and most patients treated with ESA require iron supplementation, for a stable ferritin concentration > 200 µg/L (17).

According to the KDIGO guidelines from 2012, in adult patients with CKD and anemia, who are not being treated with iron or ESA, it is suggested to try i.v. iron administration (in patients without dialysis, it is possible to attempt oral treatment for 1–3 months) when TSAT ≤ 30% and ferritin concentration ≤ 500 µg/L, if the goal is to increase HGB concentration without starting an ESA treatment (19). In adult patients with CKD treated with ESA, without iron supplementation, it is suggested to attempt i.v. iron administration (in patients who do not undergo dialysis alternatively oral formulations can be used for 1–3 months) if TSAT ≤ 30 % and ferritin concentration ≥ 500 µg/L. In patients with CKD not undergoing dialysis and requiring iron supplementation it is recommended to administer iron i.v. if the goal is to increase HGB concentration, or to lower the ESA. In patients with CKD not undergoing dialysis and requiring iron supplementation, it is necessary to choose administration route...
Table 1. Characteristics of intravenous iron preparations.

<table>
<thead>
<tr>
<th>Active substance</th>
<th>HMWID</th>
<th>LMWID</th>
<th>IG</th>
<th>IS</th>
<th>FCM</th>
<th>FO</th>
<th>FI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brand name</td>
<td>Imferon</td>
<td>CosmoFer</td>
<td>Ferrlecit</td>
<td>Venofer</td>
<td>Ferinject</td>
<td>FeraHeme</td>
<td>Monofer/</td>
</tr>
<tr>
<td></td>
<td>Dexterrum</td>
<td>INFeD</td>
<td></td>
<td></td>
<td>Injectafer</td>
<td>Rienso</td>
<td>Monover/</td>
</tr>
<tr>
<td>Carbohydrate shell</td>
<td>Dextran- branched polysaccharides</td>
<td>Dextran- branched polysaccharides</td>
<td>Gluconate- monosaccharide</td>
<td>Sucrose- disaccharide</td>
<td>Carboxymaltose- branched polysaccharide</td>
<td>Polyglucose sorbitol carboxymethyl ether</td>
<td>Isomaltoside- linear oligosaccharide</td>
</tr>
<tr>
<td>Molecular weight [kDa]</td>
<td>265</td>
<td>165</td>
<td>289–440</td>
<td>30–60</td>
<td>150</td>
<td>750</td>
<td>150</td>
</tr>
<tr>
<td>Plasma half-life (h)</td>
<td>60</td>
<td>20</td>
<td>1</td>
<td>6</td>
<td>16</td>
<td>15</td>
<td>20</td>
</tr>
<tr>
<td>Direct transferrin donation in % of administered dose</td>
<td>1–2</td>
<td>1–2</td>
<td>5–6</td>
<td>4–5</td>
<td>1–2</td>
<td>&lt;1</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Maximum single dose</td>
<td>20 mg/kg BW</td>
<td>20 mg/kg BW</td>
<td>125 mg</td>
<td>200 mg</td>
<td>15 mg/kg BW but ≤1000 mg</td>
<td>510 mg</td>
<td>20 mg/kg BW</td>
</tr>
<tr>
<td>80 kg male</td>
<td>1600 mg</td>
<td>1600 mg</td>
<td>125 mg</td>
<td>200 mg</td>
<td>900 mg</td>
<td>510 mg</td>
<td>1600 mg</td>
</tr>
<tr>
<td>60 kg female</td>
<td>1200 mg</td>
<td>1200 mg</td>
<td>125 mg</td>
<td>200 mg</td>
<td>900 mg</td>
<td>510 mg</td>
<td>1200 mg</td>
</tr>
<tr>
<td>One dose iron repletion</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Infusion 1 h</td>
<td>No</td>
<td>No ^1</td>
<td>^2(NA)</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Test dose ^1</td>
<td>Yes</td>
<td>Yes</td>
<td>?</td>
<td>Europe - yes USA - no</td>
<td>No</td>
<td>No, but it’s necessary to wait 60 min after administration</td>
<td>No</td>
</tr>
<tr>
<td>Iron concentration mg/mL</td>
<td>50</td>
<td>50</td>
<td>12.5</td>
<td>20</td>
<td>50</td>
<td>30</td>
<td>100</td>
</tr>
<tr>
<td>Available in Poland</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Life threatening AR (×10⁶ doses)</td>
<td>11.3</td>
<td>3.3</td>
<td>0.9</td>
<td>0.6</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

^1Test dose is no longer recommended by the European Medicines Agency (2013); ^2LMWID can be safely applied in a dose of 1000 mg within 1 h (47); ^3Initial studies show that FO can also be administered in a single dose of 1020 mg (28).
depending on the iron deficiency level, availability of the i.v. route, response to previous oral iron treatment, adverse reactions to orally or i.v. administered iron, compliance and cost. In the course of further iron administration in patients with CKD, it is necessary to follow the response to previous iron treatment in scope of HGB concentration. It is also necessary to monitor current blood loss, iron status tests (TSAT and ferritin), HGB concentration, ESA response and ESA dose in patients who receive these agents, change trends for all of these parameters and the clinical state of the patient. I.v. iron administration should be avoided in patients with an active systemic infection (19).

According to the opinion of the ERBP (European Renal Best Practice) from 2013 regarding the use of iron in anemia treatment in adult patients with CKD-related anemia, not treated with iron or ESA, it has been suggested to apply iron treatments (i.v. or, if well tolerated, orally as a first treatment stage in patients who do not undergo dialysis particularly in stage 2 or 3 of CKD, or in patients who undergo peritoneal dialysis) if there is substantial iron deficiency (TSAT < 20% and ferritin < 100 µg/L) or if it is desirable to increase the HGB concentration, without starting ESA treatment, when TSAT < 25% and ferritin concentration < 200 µg/L in patients who do not undergo dialysis, or when TSAT < 25% and ferritin concentration < 300 µg/L in patients who do undergo dialysis (20). During iron treatment, no attempts should be made to increase TSAT > 30% and ferritin concentration in serum > 500 µg/mL, both in dialysed and non-dialysed CKD patients. In patients with CKD treated with ESA and not receiving any iron supplements, it is suggested to attempt intravenous iron treatment (patients not on dialysis should begin oral treatment, if well tolerated), if it is desirable to increase HGB concentration or decrease the ESA dose, when TSAT < 30%, and ferritin concentration < 300 µg/L. In patients who undergo hemodialysis, with a high ferritin concentration in plasma and an insufficient response to ESA, or with a benefit-risk ratio negative for an ESA treatment, an i.v. series of iron doses could be applied. In dialysis patients treated at the same time with iron preparations and ESA, it is suggested to remain careful while increasing the ferritin concentration > 500 µg/L, especially when the TSAT value is appropriate (> 30%) (20).

**Ferumoxytol (FO)**

In a multicenter randomized, open-label phase 2 study, comparing safety and efficacy of FO and IS, 162 patients with CKD have been randomized into two groups in 1 : 1 ratio. One group received FO 1.02 g (2 injections of 510 mg), patients in the other group received 1 g IS in slow releasing injections or infusions (10 doses for dialysis patients and 5 doses for non-dialysis patients) (21). Primary endpoint was the change of hemoglobin concentration after 5 weeks and it was 0.8 ± 0.1 g/dL for the group receiving FO and 0.7 ± 0.1 g/dL for patients, who were being administered IS). The adverse reaction profile for FO in comparison to IS was following: all ARs, accordingly 48% vs. 65%, drug-related ARs 10% vs. 16% and these were single cases of anaphylactic reactions, dysgeusia, feeling hot, headache, injection site hemorrhage, nausea in group FO. In the IS group, the following has been observed: hypotension (6 episodes in 3 patients), parosmia (30 episodes in 3 patients), diarrhea (2 episodes in 1 patient), injection site pain (2) and single cases of feeling hot, cold sweat, myalgia and unresponsiveness to stimuli (1). ARs leading to treatment discontinuation occurred in 1% vs. 5%. Severe ARs (SARs) occurred in 9% vs. 7%, and SARs related to the medicine were 1% vs. 1% (21).

In a phase 3 study, 304 patients with CKD were randomized in a ratio 3 : 1 to the group receiving accordingly FO 2 × 510 mg i.v. in intervals of 5 ± 3 days, or everyday for 21 days 200 mg of elementary iron orally (22). Primary endpoint was the increase of HGB on day 35, which was 0.82 ± 1.24 g/dL in the group administered FO and 0.16 ± 1.02 g/dL in patients receiving iron orally. In the group not treated with ESA, HGB increased accordingly by 0.62 ± 1.02 g/dL vs. 0.13 ± 0.93 g/dL. However, in patients treated with ESA, HGB in the studied groups increased accordingly by 1.16 ± 1.49 g/dL vs. 0.19 ± 1.14 g/dL. ARs occurred in 10.6% of patients treated with FO and 24% of patients treated with orally administered iron. No SARs have been observed.

Auerbach et al. have also researched the safety and efficacy of the FO 1020 mg dose administered in a single injection, lasting < 15 min in 60 patients with IDA (HGB < 11 g/dL, TSAT ≤ 20%, ferritin < 100 µg/L) and intolerance to oral iron preparations (23). Patient’s vital parameters have been monitored for an hour after administration of FO, later information on adverse reactions has been gathered by phone on days 1, 2 and 7. No SARs have been reported. Patients (26 - 43.3%) have experienced adverse reactions, in 13 patients they were mild and self-limiting during infusion, 14 patients reported joint and muscle pain and/or headache within 246-48 h after FO administration. The starting HGB concentration level in studied
patients was 9.4 g/dL, an approximate increase after 4 and 8 weeks was 2.1 and 2.6 g/dL, respectively. Based on these observations, administration of FO in a single 1020 g dose, in ≤ 15 min appears to be safe and effective (23).

**Ferric carboxymaltose (FCM)**

A 56 week, open-label, multicenter, prospective, randomized three-arm study FIND-CKD, has attempted to determine the optimal administration route and dose of iron in patients with IDA and CKD, not requiring renal replacement therapy. Patients (626) were randomized to 3 groups in proportion 1 : 1 : 2 (24, 25). The first group received i.v. 1000 mg FCM with additional doses if necessary, to achieve serum ferritin level of 400-600 µg/L. The second group was treated i.v. with 200 mg FCM, with additional doses if necessary, to achieve ferritin concentration of 100-200 µg/L. The third group has been advised to take orally 200 mg of ferrous sulfate (FS) every day. Primary endpoint was time to initiation of additional anemia treatment (ESA therapy, application of another iron preparation, or blood transfusion) and concentration of HGB in two consecutive samples < 10 g/dL, without the increase by ≥ 0.5 g/dL in the period of 8-56 weeks. In the studied groups, the primary endpoint was achieved in 36 (23.5%), 49 (32.2%) and 98 (31.8%) patients, respectively (HR 0.65; 95% CI: 0.4–0.95; p = 0.026). All groups achieved an HGB increase, however, in comparison to the orally administered preparation, the HGB increase was significantly higher in the first group receiving i.v. FCM, until achieving ferritin concentration of 400-600 µg/L (p = 0.014). The highest percentage of patients who have achieved a HGB increase of ≥ 1 g/dL (56.9%) was in the first group, compared to the second group treated intravenously (34.2%) and the third group treated orally (32.1%) (HR 2.04; CI: 1.52-2.72; p < 0.001). ARs and SARs were similar in all groups. The authors concluded that in comparison to oral iron, intravenous administration of FCM with a ferritin concentration level of 400-600 µg/L allowed for a faster increase and then maintaining the HGB concentration and delayed the need for other anemia treatment, including ESA. No renal toxicity has been observed in the study, with no difference in heart or infectious events (24, 25).

The REPAIR-IDA study also refers to the population of CKD patients with IDA, not requiring renal replacement therapy (26). This multicenter, randomized study compared intravenous FCM to oral FS and assessed their efficacy and safety for the cardiovascular system. A total of 2584 participants have been randomized into a group receiving 2 doses of 750 mg FCM in weekly intervals, or into a group receiving 5 doses of FS 200 mg within 14 days. After 56 days of observation, in comparison with FS, in the group receiving FCM greater increase in HGB concentration was achieved (1.13 vs. 0.92 g/dL; 95% CI: 0.13–0.28), also a higher percentage of participants achieved an increase of HGB ≥ 1 g/dL (48.6 vs. 41%). There were no significant differences between the studied preparations in regard to the safety profile, including serious heart events, death, myocardial infarction, or stroke. In the FCM group there were more frequently observed hypertensive episodes usually passing without further intervention (26).

An interesting study comparing intravenous administration of FCM and oral administration of FS was performed by Onken et al. on patients with IDA of different etiology (27). After 14 days of oral iron administration, 507 patients with inadequate treatment response (HGB increase < 1 g/dL, cohort 1) have been randomly added to group A (2 FCM doses, each 750 mg in 7 day intervals) or to group B (oral FS 325 mg 3 times a day, for 14 days continuously). Other patients (504) with insufficient iron supplementation (cohort 2) have been added to group C (2 FCM doses, each 750 mg, in 7 day intervals) or to group D (iron sucrose – IS). Primary endpoint for efficacy was the change of HGB concentration form the starting point until day 35 of observation, or until intervention (blood transfusion, additional iron use, increased ESA dose). Primary endpoints regarding safety was mortality for any reason, myocardial infarction not resulting in a death, cerebral stroke, unstable angina pectoris, heart failure, arrhythmia and hypotension or hypertension. The average HGB increase was higher in group A than in group B (1.57 ± 1.19 g/dL vs. 0.8 ± 0.8 g/dL; p = 0.001). Post hoc comparison of groups C and D also demonstrated higher efficacy of FCM (2.9 ± 1.64 g/dL vs. 2.16 ± 1.25 g/dL; p = 0.001). Safety endpoints occurred in 3.4% of patients receiving FCM versus 3.2% in the compared group (27).

Another randomized study on 160 patients with IDA (HGB ≤ 11 g/dL, ferritin ≤ 100 or ferritin ≥ 300 µg/L and TSAT ≤ 30%) compared the safety and efficacy of 2 doses 750 mg FCM (n = 82) with iron dextran (DEX) (n = 78) (9). The researchers had the freedom to apply HMWID (Dexferrum) or LMWID (INFeD). Most patients received HMWID. Compared to the group receiving FCM, the patients receiving DEX more often experienced immune system disorders (0 vs. 10.3%, p = 0.003), including 7 cases of hypersensitivity (9%) and skin disorders.
(pruritus, rash, urticaria) (7.3 vs. 24.4%, p = 0.004). In the FCM group participants more often experienced asymptomatic hypophosphatemia (8.5 vs. 0%; p = 0.014) and gastrointestinal ARs as diarrhoea, nausea, vomiting (29.3 vs. 17.9%; p = 0.099). ARs of the nervous system (dizziness and headache) occurred in a similar number of participants (19.5 vs. 21.8%; p = 0.845). In both groups (FCM vs. DEX) there was a similar increase in HGB concentration (accordingly 2.8 g/dL and 2.4 g/dL; p = 0.2). This study confirms earlier suggestions that the administration of DEX has resulted in a more frequent occurrence of hypersensitivity reactions (9). The researches have explained the freedom of choice of DEX preparation (HMWID or LMWID) by their differences in the iron core, and the dextran shell is responsible for immunogenicity, since its amount is similar in both products. Previous 2 studies comparing HMWID and LMWID showed higher frequency of anaphylactic reactions with the use of HMWID (28, 29), while in another study, a similar or higher frequency of anaphylactic reactions is demonstrated after administration of LMWID (30).

Ferric isomaltoside 1000 (FI)

In a multicenter, open-label study, Wikstrom et al. researched the safety of ferric isomaltoside 1000 (FI) in CKD patients (31). The impact on IDA parameters was the secondary endpoint. In this study 182 CKD patients (161 on dialysis and 21 in the pre-dialysis period) have been administered FI intravenously in the form of 4 boluses, 100-200 mg of iron per dose, or as a fast, single infusion of the total dose calculated according to the Ganzoni formula. Eighty two percent of study participants were treated with ESA, and its dose was not modified during the study. Some patients had to switch from previously applied iron preparations to FI (n = 144), others have not been taking earlier any iron preparations (38 patients). For a period of 8 weeks, frequency of ARs was monitored and markers of IDA were measured. Nineteen ARs related to the medicine occurred in 13 patients (7.1%) after 584 administrations (3.3%). Abdominal pain, dysphonia, nausea, and headache were observed most often. There were 2 SARs – unstable angina pectoris and sepsis of *Staphylococcus aureus* etiology, however their relation to the FI treatment remained unclear. Neither acute anaphylaxis, nor delayed anaphylactoid reactions were reported. There were also no significant changes in laboratory tests or vital parameters. After 8 weeks, HGB increased in average from 9.92 ± 0.9 g/dL to 11.12 ± 1.47 g/dL in patients previously untreated with iron (p = 0.001). In patients who were previously treated with iron preparations, there was a small increase, or a stabilization of HGB level. Ferritin concentration in plasma, iron and TSAT increased significantly during all control visits (31).

**Anemia in women**

Iron deficiency is common in women at reproductive age. During pregnancy, daily demand for iron increases from 1.5-2 mg to 5-7 mg/day. The incidence of IDA in pregnant women in industrialized countries is approximately 17.4% while in developing countries it is estimated to be at a 56% (35-75%) level (32). Perinatal anemia caused by iron deficiency is related to a significantly higher morbidity of mother and fetus. Ferritin concentration is an indicator of iron deficiency ≥ 30 µg/L. HGB concentration < 8.5 g/dL increases chances of a premature birth or low weight of the newborn. Low concentration of HGB before birth is a risk factor for postnatal hemorrhage and severe bleeding. Oral iron supplementation results in a slow and often suboptimal treatment response, or can be badly tolerated. Blood transfusions are connected with commonly known risks. A quick intravenous supplementation can prevent the need for a blood transfusion or decrease the amount of administered blood preparations and significantly improves compliance (5).

**Safety and efficacy of FCM in IDA treatment** (HGB < 11.5 g/dL) in 65 women in 2. and 3. pregnancy trimester, have been assessed by Froessler et al. in an observation, prospective study, in which the participants were administered FCM in a dose of 15 mg/kg BW between 24th and 40th week of pregnancy (33). In this study, a significant HGB concentration increase was achieved after 3-6 weeks, lasting for 8 weeks since the administration of FCM. Ferritin concentration increased as well. Fetus heart rate was monitored during drug infusion and no negative impact of FCM on the fetus has been observed. Nineteen out of 26 patients declared improvement in compliance (5).

**Safety and efficacy of FCM in IDA treatment** in a randomized study, 174 women with postpartum anemia were intravenously administered FCM in an average dose of 1.4 g, and 178 participants have taken orally 375 mg of FS 3 times a day.
for 6 weeks (34). Compared to FS, patients who received FCM had a faster increase of HGB > 2.0 g/dL (7 vs. 14 days; \( p < 0.001 \)), significantly more patients had a HGB increase > 3.0 g/dL (86.3 vs. 60.4%; \( p < 0.001 \)), also more participants experienced stabilization of the HGB concentration > 12 g/dL (90.5 vs. 68.6%; \( p < 0.001 \)). No serious ARs have been observed in both groups (34).

In another randomized study, to assess safety and efficacy of intravenous FCM in the treatment of postpartum anemia compared with an orally administered FS, 227 women received FCM (depending on individual needs, doses ≤ 1000 mg were repeated weekly, at most 3 times, in average 1.3 g), 117 participants were taking FS (2 × daily 100 mg of elemental iron) (35). In this study, FCM was as effective as FS in increasing HGB concentration. In the FCM group the increase in ferritin concentration was significantly greater (\( p < 0.0001 \)), which indicates a successful replenishment of iron store in organism (35).

Another multicenter, randomized study included 291 women directly after delivery with HGB concentration > 12 g/dL (vs. 7 g/dL) (73% vs. 52.7%; \( p < 0.001 \)) and 144 a placebo). Fatigue reduction has been observed in accordingly 65.3% vs. 52.7% of patients (OR 1.68, 95% CI 1.0 × 52.7; \( p = 0.03 \)). Symptom reduction (50%) in the Piper scale has been achieved in 33.3% of women who have been administered FCM and in 16.4% of participants who have taken a placebo (\( p < 0.001 \)). On day 56 after the administration of FCM all women had a HGB concentration ≥ 12 g/dL (vs. 87% at the baseline), while in the placebo group the percentage of participants with HGB concentration ≥ 12 g/dL has decreased from 86 to 81%. Mental quality of life and cognitive functions improved better in the FCM group. Improvement of attention was better in the first group with baseline ferritin concentration of < 15 µg/L. The number of reported ARs in the FCM groups, compared to the placebo group was 209 vs. 114, respectively, these were mostly headache, nasopharyngitis, pyrexia and nausea, they were mild or moderate.

**Heart failure**

In a 24-week FAIR-HF study, on a group of 459 patients with heart failure (NYHA II and EF ≥ 40% or NYHA III and EF ≤ 45%) and with iron deficiency (ferritin < 100 µg/L or ferritin 100-300 µg/L and TSAT < 20%), with the HGB concentration 9.5ñ13.5 g/dL, comparing FCM to a placebo (ratio 2 : 1), has indicated that weekly 200 mg FCM doses, repeated until replenishment of iron deficiency, and then every 4 weeks, resulted in diminished disease symptoms (50 vs. 28%) (39). Heart failure symptoms NYHA I or II were present in 45% patients on FCM and in 30% patients from the placebo group. The results were similar in patients with anemia, as well as in those without anemia. In the FCM group significant improvement in the 6 minute walking test and quality of life was noticed. Rates of death, ARs and SARs were similar in both groups.

Another multicenter, open-label, pilot, 8-week study evaluated the safety of FI as a single dose for iron deficiency correction, in accordance with the Ganzoni formula (target HGB 13 g/dL; mean dose 868 mg, range 650-1000 mg) in 20 patients with...
Inflammatory bowel disease

About 1/3 of patients with IBD experience anemia and this significantly diminishes their quality of life (5). Anemia is caused by loss of iron as well as a prolonged inflammation. Indication for intravenous iron administration in this group is HGB < 10 g/dL, intolerance or ineffective treatment with an oral preparation, high intensity of inflammatory bowel changes, use of ESA and patient’s preference. It is recommended to use TSAT for monitoring the efficacy of intravenous iron administration and to continue treatment until TSAT of 50% is achieved. 

In a large multicenter, randomized study comparing safety and efficacy of two intravenous iron preparations – FCM and IS, in a group of 485 patients with mild or moderate IBD and IDA, 240 patients were administered a maximum of 3 doses of FCM 1000 or 500 mg, and a group of 235 participants received 11 IS infusions of 200 mg, the total dose was calculated in accordance with the Ganzoni formula (41). Compared to the IS group, more patients treated with FCM achieved an increase in HGB concentration ≥ 2 g/dL (65.8 vs. 53.6%, p = 0.004) and the stabilization of HGB level (72.8 vs. 61.8%, p = 0.015). Both preparations improved quality of life and were well tolerated. Departures from the drug administration regime were more frequent in the IS group.

In a 8-week, multicenter, open-label, prospective, randomized, non-inferiority study with 338 participants, intravenous FI was compared with oral FS in the treatment of IDA in patients with IBD (mild or during remission) with a HGB concentration of < 12 g/dL and TSAT < 20% (7). The patients with identified intolerance to orally administered iron were excluded from the study. The participants have been randomly divided in a 2 : 1 ratio to group A – intravenous FI (225 patients) and group B – oral FS (113 patients), 200 mg of elemental iron daily for 8 weeks. Additionally, patients from group A were randomly divided into group A1 that received weekly 1000 mg FI i.v. as 15-min infusion until achieving target iron dose, and group A2, which received 500 mg FI i.v. as a 2-min bolus, until achieving the calculated dose. Primary endpoint was the change in HGB concentration from baseline to week 8. Secondary endpoints were changes in the HGB concentration to weeks 2 and 4, change in ferritin concentration and TSAT to week 8, a number of patients who did not finish the study due to lack of efficacy or ARs, changes in life quality to weeks 4 and 8, and safety. To week 8 the trend in HGB concentration increase was higher after FS compared to FI. In patients administered FI i.v. compared to patients receiving FS orally, the increase of ferritin was higher by 48.7 (95% CI: 18.6–78.8; p = 0.002), while the TSAT increase was lower -4.4 (95% CI: -7.4– -1.4; p = 0.005). There were no differences in quality of life and safety profile between tested groups. All ARs occurred in 42, 37 and 35% of patients, respectively, drug-related ARs in 15, 12 and 10% of patients. In group A it was flushing, hypotension, respiratory distress, itching, rash, tightness in the chest, anxiety, and disturbances of vision during the administration of the drug. One SAR occurred in group A1 – an intensive epilepsy attack. All symptoms resolved on their own, without any negative consequence. No serious symptoms of hypersensitivity, or hypophosphatemia were observed. The percentage of patients who achieved a HGB increase > 2 g/dL in the FI and FS group was accordingly 67 and 61%, respectively (p = 0.32). FI was more effective in case of higher concentration doses > 1000 mg where the HGB increase > 2 g/dL has been observed in 93% of patients. The baseline HGB concentration and CRP concentration were important HGB increase indicators after intravenous iron administration. The researchers suspect that in their study the total iron demand was underestimated, they also stressed that it is necessary to take into account the baseline HGB concentration and CRP level (42).

In a meta-analysis of 14 randomized studies comparing FCM (n = 2348) with other iron preparations – oral (n = 832) or intravenous IS (n = 384), or a placebo (n = 762), in patients with IDA in the course of CKD, with blood loss in obstetrics and gynecology, gastrointestinal tract diseases, after the calculation of the iron deficit in accordance to the Ganzoni formula, a maximum dose of 1000 mg iron per week has been administered for 1-24 weeks (43). In comparison with the most often compared product – oral iron, FCM was more effective. The mean end-of-trial increase after FCM treatment over oral iron was, for
HGB concentration 4.8 g/L (95% CI: 3.3-6.3 g/L), for ferritin level 163 µg/L (95% CI: 153-173 µg/L) and for TSAT 5.3% (95% CI: 3.7-6.8%). The number of SARs and deaths were similar in all groups, however the frequency of constipation, diarrhoea, nausea and vomiting, was lower than in patients who were taking iron preparations orally (44).

**Cancer**

Another group of patients, who could benefit from an iron treatment are cancer patients (5). Anemia in this group is a result of therapy, as well as concomitant anemia of chronic diseases. European guidelines recommend to begin treatment at an early stage, with HGB concentration of 9-11 g/dL and to maintain the HGB ≤ 12-13 g/dL. In the USA, ESA is being used to achieve a maximum of HGB 10 g/dL, as there are suggestions saying that a higher HGB concentration can lead to progress of cancer, however other studies suggest that cancer progression can be a result of ESA impact on tumor cells. There is no evidence confirming that oral iron preparations increase ESA efficacy in oncology, however intravenous administration has this result (5).

Steinmetz et al. in their study investigated the efficacy and safety of FCM in routine anemia treatment of cancer patients (45). Out of 639 participants, 619 received mean 1000 mg FCM (range 600-1500 mg). Four hundred twenty participants had a baseline HGB concentration evaluated and 364 patients had at least one control measurement of HGB level. After the administration of FCM, compared to the combination of ESA + FCM, a similar increase of HGB was achieved – accordingly 1.4 g/dL (0.2-2.3 g/dL; n = 233) vs. 1.6 g/dL (0.7-4 g/dL; n = 46). Patients with a baseline HGB ≥ 11 g/dL and ferritin ≥ 500 µg/L benefited from FCM treatment (stable HGB ≥ 11 g/dL). Also patients with ferritin concentration ≥ 500 µg/L, but low TSAT, benefited from the FCM treatment. FCM was well tolerated, 2.3% patients reported ARs related to the drug. The researchers emphasized that a significant increase of HGB concentration and its stabilization in the range of 11-12 g/dL in patients treated with FCM indicated the importance of intravenous iron preparations in treatment of anemia in cancer patients.

Batist et al. have proven that *i.v.* administration of iron, in comparison with oral preparations significantly increases HGB concentration, hematopoiesis, decreases the time to achieve target HGB concentration and significantly decreases the number of blood transfusions (46).

In another study, Pedrazzoli et al. analyzed the use of ESA and iron in comparison with ESA alone, in patients with solid tumors, treated with chemotherapy with concomitant anemia and no iron deficiency (47). A statistically significant improvement was achieved in the group, which received iron. In non-responder cases, the ESA dose has been doubled after 4 weeks and a response has been achieved in 68.2% of iron and ESA patients, compared with 32% in the ESA only group.

**CONCLUSIONS**

Iron deficiency anemia is an important clinical problem, impacting many people. Oral iron administration is the treatment of choice. Unfortunately, this therapy is often insufficient due to bad absorption, adverse reactions, or the need for a fast replenishment of large demand. New iron preparations (FCM, FO, FI) allow for an effective replenishment of an existing iron deficit even with 1–2 infusions, without the need for a test dose, which significantly improves compliance.

The safety profile is acceptable, however patients with SARs after administration of older generation intravenous iron in the past were excluded from trials. In the studies mentioned in this paper, even over half of the patients have experienced adverse reactions, these were, however, mild or moderate, and were not always drug-related. Serious adverse reactions occurred in single cases. Life threatening adverse reactions have been rare, since HMWID was withdrawn from use, but each drug administration can lead to potentially dangerous adverse reactions, even with good tolerance of previous infusions. The main concerns are connected mostly with risk of hypersensitivity reactions. In 2013 European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use (CHMP) issued recommendations to manage risk of allergic reactions related to intravenous iron-containing medicines. After analysis of the published literature, data from pre- and clinical trials and post marketing experience, CHMP concluded that although there is some risk of hypersensitivity reactions in very rare cases leading even to death, the benefit-risk ratio is in favor of intravenously administered iron since the benefits prevail over the risks in the treatment of iron deficiency if the oral administration is unsatisfactory or badly tolerated (48).

According to CHMP, test dose is no longer recommended, because its good toleration does not guarantee safety of full dose. Therefore, the patient needs to be monitored by qualified personnel during
the infusion and for 30 min after, with easy accessibility to resuscitation equipment. Thus, the possibility of reducing the incidence of drug administration by administering a single, repletion dose is noteworthy mostly because of patient’s comfort and lowered personnel work cost. Medical professionals should immediately terminate the administration of iron and regard adequate treatment whenever hypersensitivity reaction occurs. This is why patient should be monitored for symptoms of hypersensitivity reactions in the course of and for at least 30 min following the administration. Intravenous iron preparations should not be administered in patients with hypersensitivity to a specific active substance, excipients or other parenteral iron products. Patients with allergies or immune and inflammatory conditions and with history of severe asthma, eczema or other atopic allergies are more vulnerable to hypersensitivity. Intravenous iron administration should not be used during pregnancy unless it is absolutely necessary, and its use should be restricted to the second or third trimester. The benefits of treatment should obviously prevail over the potential risks to the fetus (43, 48).

In literature there are no studies comparing new intravenous iron preparations. Long-term results of such treatment are also unknown. A common fear of use of intravenous iron preparations due to safety concerns is also a result of misinterpretation of non-threatening adverse reactions related to infusion of the medicine and incorrect or unnecessary use of anti-allergic drugs, in available literature, mostly diphenhydramine, and its side effects could be incorrectly attributed to the parenteral iron preparations (4). Intravenous administration of iron preparations is related to at least a short-term oxidation stress, but there is neither precise tool for its measurement, nor data referring to clinical implication of this phenomenon. Also, there is no definite evidence for an increased risk of infection after use of intravenous iron preparations, however it is recommended to avoid their use in patients with an active infection (8). An important aspect is also cost effectiveness. The price of new iron preparation is higher, but drug can be cost effective due to shorter administration time and lower infusion frequency. Additionally, it is important to realize that due to the structure of new iron preparations, there is no possibility to remove them in the process of hemodialysis (13). Currently, there is a need for longer observation and more studies, to better assess efficacy and safety profiles of new intravenous iron products. Another problem are side effects of iron used outside its approved indications. Excessive iron use leads to its accumulation in vital organs and is responsible for their dysfunction and many health complications (49, 50). This issue will be a topic of next publication.

REFERENCES


Received: 2. 12. 2015