Annals of Hematology & Oncology

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Austin Publishing Group

Review Article

Modern Intravenous Iron Therapy: A Review on Safety and Practical Aspects

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Received: October 27, 2022; **Accepted:** November 26, 2022; **Published:** December 03, 2022

Abstract

Introduction: Intravenous iron formulations have been approved in Europe and North America for the treatment of iron deficiency if oral iron is not tolerated or not efficacious. Recently-developed intravenous iron formulations exhibit specific physicochemical and immunological properties, with distinct bioavailability, efficacy and safety profiles.

Area of Interest: intravenous iron formulations safety and tolerability were reviewed in the framework of a Swiss expert meeting. This work focused on the specificity of each compound with emphasis on the practical aspects of its use.

Expert Opinion: Adverse reactions in response to iv formulations can be categorized into two main types: hypophosphataemia and hypersensitivity. Hypophosphatemia follows administration of ferric carboxymaltose at a higher rate in comparison to other formulations, but is mostly mild, transient and asymptomatic. However, the decrease in serum phosphate following repeated administration of iron preparations can affect bone health, particularly in patients at risk for osteomalacia. Severe hypersensitivity reactions are the most life-threatening adverse reactions to intravenous iron supplementation. Iron (III)-isomaltoside 1000 seems to induce severe hypersensitivity more often (RR 5.6 - 16.2) than ferric carboxymaltose. Further studies are needed to address issues of long-term safety in high dose and prolonged administration of intravenous iron preparations in case of chronic diseases.

Keywords: Iron; Intravenous; Efficacy; Haemoglobin; Anaemia; Safety; Hypophosphatemia; Hypersensitivity

Abbreviations

AE: Adverse Events; CHF: Chronic Heart Failure; CKD: Chronic Kidney Disease; Hb: Haemoglobin; IBD: Inflammatory Bowel Disease; ID: Iron Deficiency; IDA: Iron Deficiency Anaemia; IV: Intravenous; SD: Standard Deviation

Introduction

It took several decades to transform a highly toxic colloidal solution of Intravenous (IV) ferric hydroxide that had elicited

Citation: Juillerat P, Angelillo-Scherrer A, Surbek D, Restellini S, Biedermann L, Rogler G, et al. Modern Intravenous Iron Therapy: A Review on Safety and Practical Aspects. Ann Hematol Oncol. 2022; 9(6): 1413.

severe adverse reactions into commercially available parenteral iron preparations that enable high doses of IV iron to be administered in a short lapse of time and with a comparatively low risk of adverse effects. Iron (III) sucrose, one of the first commercially available intravenous iron compounds, went into clinical use in Europe in 1949 [1]. High molecular weight iron dextran followed in the 1950s but its usage was stopped due to anaphylactic reactions following administration, except in clinical conditions offering no alternative [2]. In 1977, IV administration of ferric gluconate [3], and in the 1990s low molecular weight iron dextran went into clinical use, the latter with a lower risk of severe adverse drug reactions [4]. Near 2000, three "new- or third-generation" iron preparations entered clinical use: ferumoxytol, ferric carboxymaltose and iron (III)-isomaltoside 1000. Their high stability enables a total replacement dose to be administered in just one or two infusions. Nevertheless, each of these products exhibits particular physicochemical and immunological properties which have led to distinctive clinical outcomes and safety profiles [5]. This review focuses on ferric carboxymaltose and iron (III)-isomaltoside 1000 as the current "new generation" IV iron preparations mainly used in Europe. It is out of the scope of this article to provide practical approaches regarding diagnosis of ID and detailed advises on its treatment in specific therapeutic areas.

Physicochemical and Immunological Properties of Intravenous Iron

All IV iron preparations are colloidal suspensions of nanoparticles. They consist of a polynuclear core of iron (III) oxyhydroxide surrounded by a carbohydrate ligand ("shell"). The carbohydrate shell stabilizes the core and thus protects against further polymerization. The shell also slows the continuous release of bioactive iron, which is toxic at excessive concentrations leading to oxidative stress [6,7]. Parenteral iron products qualify as non-biological complex drugs because their level of complexity exceeds small synthetic drugs by far. They are, however, less complex than molecules produced in living systems, such as antibodies. Nevertheless, iron core and iron shell carbohydrate complexes are intricate, unique and difficult to manufacture [8]. They require very specific conditions and a highly controlled and sophisticated environment for their production. Thus, the smallest variation in the manufacturing process, such as changes in pH, temperature, material sources, or reaction time could critically influence the physicochemical characteristics and properties of the final product, including molecular weight or particle size distribution, valence state of iron, surface charge, or crystallinity [8]. The resulting structures of the iron core and iron shell, as well as the size and size distribution of the particles affect bioavailability, toxicity and clinical features of IV iron preparations [9,10].

Efficacy and Clinical Outcomes

Data from head-to-head trials on the efficacy of different iv iron formulations is limited. (Table 1) summarizes effects and indirect comparisons of IV iron formulations, mainly based on network meta-analyses [11-14]. Clinical potency of distinct IV iron formulations can differ depending on the specific indication for therapeutic use and the clinical outcome selected. Thus, iron (III) isomaltoside has shown a higher increase of hemoglobin from baseline compared to ferric carboxymaltose in anaemic patients intolerant to oral iron, but failed to show superiority among those patients with an increase in haemoglobin of ≥ 2g/dL [12]. Ferumoxytol and ferric carboxymaltose at monthly doses of 1020 mg and 750-1500 mg, respectively, were shown to be particularly potent in anaemic patients with Chronic Kidney Disease (CKD) [11]. Indirect comparisons with other intravenous irons based on studies using oral iron as a control indicate that ferric carboxymaltose might show superiority over other iv iron formulations regarding haemoglobin increase [15]. In IBD patients, only ferric carboxylmaltose, but not iron (III) sucrose or iron (III) isomaltoside 1000, has shown statistically significant superiority versus oral iron [12]. This data is specific for patients with IBD and may not apply to IDA from other causes. Considering many uncertainties about distinct efficacy and outcomes of different preparations, further head-to-head trials are needed in order to provide better evidence regarding the efficacy of different IV iron formulations [12].

Safety of Intravenous Iron Formulations

Toxic reactions to free iron, hypersensitivity, and hypophosphatemia are the three most relevant side effects of IV iron formulations. Anaphylaxis is a dose-independent severe hypersensitivity reaction historically associated with iron dextran [15,16]. Reactions to free iron are also dose-dependent and present with hypotension, nausea, vomiting, abdominal and back pain [17]. Smaller molecular weight iron preparations such as ferric gluconate and iron (III) sucrose have a shorter half-life, are less stable and therefore release higher amounts of "free" iron into the circulation after high dose administration [18]. Moreover, non-transferrin bound iron (i.e., free iron) may also catalyse production of reactive oxygen species that then leads to oxidative stress and cellular damage [19]. Thus, the extent of free iron released into the circulation is one of the major determinants of the maximally tolerable single dose for each iron formulation and its administration rate. In other words, the higher the fraction of free iron, the lower the maximal dose and/or the longer the administration duration. A particular type of reactions following administration of IV iron are the so called Fishbane reactions. They are characterized by transient flushing, truncal myalgia and arthralgia [20]. Fishbane reactions are usually not associated with symptoms of anaphylaxis such as hypotension, oedema, respiratory or gastrointestinal disorders. Fishbane reactions are believed to be triggered by labile iron, rather than being mediated by immunological mechanisms. Fishbane reactions seem to resolve following cessation of the IV iron infusion without specific treatment and are believed to not reappear upon re-challenge. However, the characterization of such reactions remains purely observational and no evidence is available regarding their risk factors and clinical relevance. Therefore, a prudent approach considering potential anaphylaxis must be taken into consideration when symptoms of a Fishbane reaction occur. Aspects related to the administration of the commonly used IV iron formulations are detailed in (Table 2).

General Safety Features

Modern IV formulations generally present a favorable safety profile with a low risk of life-threatening adverse reactions [21]. A meta-analysis of 97 clinical studies with iv iron formulations did not report an increased risk of serious adverse events compared to controls [22]. However, continued administration of IV iron preparations can potentially lead to damaging iron overload in the liver, heart

Table 1: Recent publications comparing efficacy and clinical outcomes of different intravenous iron preparations.

Publication	Method	Details	Outcomes
[13]	Indirect comparison of iron(III)-isomaltoside 1000 with ferric carboxymaltose for the treatment of iron deficiency anaemia based on randomized studies in which these iron preparations were compared to iron(III) sucrose as a common comparator	1 study with iron(III)-isomaltoside 1000 and 3 studies with ferric carboxymaltose versus iron(III) sucrose were used for the indirect comparison	1. Increase of haemoglobin from baseline: significantly higher with Iron(III)-isomaltoside (mean difference: +0.249 g/dL, Confidence Interval [CI] 0.072-0.426); 2. Fraction of patients who showed a clinically meaningful response to treatment (defined in most studies of IDA as ≥2.0 g/dL from baseline: no significant difference between iron(III)-isomaltoside 1000 and ferric carboxymaltose
[11]	Pairwise and network meta-analyses of randomized studies were used to evaluate the efficacy of various intravenous iron preparations for treatment of anaemia in chronic kidney disease	34 studies were analysed; calculations used non-response to iron supplementation, defined as (i) failure to increase haemoglobin by 0.5–1.0 g/dL, or (ii) introduction of an erythropoiesis-stimulating agent, or (iii) dose increase or switch to another iron preparation, or need for blood transfusion; Clinical potency was assessed using the surface under the cumulative ranking area	Clinical potency of iron preparations administered at particular monthly cumulative doses was as follows (starting with most potent preparation and respective monthly cumulative dose): (1) ferumoxytol 1020 mg/month; (2) ferric carboxymaltose 750–1500 mg/month; (3) iron(III) sucrose ≥400 mg/month; (4) iron(III) sucrose 100-300 mg/month; (5) iron(III)-isomaltoside 1000 500 mg/month; (6) ferric gluconate 1000-1500 mg/month; (7) iron polymaltose 500 mg/month; (8) ferric carboxymaltose 1500 mg/month; (9) iron(III)-isomaltoside 1000 1000 mg/month; (10) oral iron
[14]	Indirect comparison of the efficacy of ferric carboxymaltose versus other intravenous iron preparations in iron-deficient patients using a network meta-analysis of randomized studies, in which intravenous iron preparations were compared to oral iron (common comparator)	6 studies were included in the network meta-analysis	1. Serum ferritin (mcg/L) was significantly increased with ferric carboxymaltose compared to oral iron (delta 172.8; 95 % CI 66.7-234.4); 2. Haemoglobin (g/dL) was significantly improved with ferric carboxymaltose compared to ferric gluconate (delta 0.6; 95 % CI 0.2-0.9), oral iron (delta 0.8; 95 % CI 0.6-0.9) and placebo (delta 2.1; 95 % CI 1.2-3.0)
[12]	Indirect comparison of efficacy and safety of different parenteral iron preparations in the treatment of iron deficiency anaemia in inflammatory bowel disease using a network meta-analysis of randomized studies, in which parenteral iron preparations were compared to oral iron (common comparator)	5 studies were included in the network meta-analysis; Primary outcome was therapy response, defined as Hb normalisation or increase ≥2 g/dL	Therapy response was significantly superior with ferric carboxymaltose compared to oral iron only (Odds Ratio=1.9, 95% Credible Interval 1.1-3.2); Iron(III) sucrose and iron(III)-isomaltoside 1000 also had better response rates than oral iron, but failed to reach statistical significance

muscle and joints. Therefore, careful monitoring of iron parameters is recommended in patients who need repeated iron infusions, for example in patients with dialysis-dependent CKD [23]. Another concern is the possible induction of endothelial injury in response to IV iron preparations and to reactive oxygen species, which may accelerate atherogenesis. *In vitro* and *in vivo* data have shown high oxidative stress associated with iron (III) sucrose and ferric gluconate [24]. However, additional studies need to provide further insights into the clinical relevance of these mechanisms [21,22], especially in newer IV iron formulations.

Furthermore, risk of infection may increase because some pathogenic microorganisms thrive on iron. However, to date no increased risk of infection following iron therapy has surfaced [22]. In the absence of an urgent clinical need, IV iron should however be avoided in patients with acute infection.

In pregnancy, iron deficiency (ID) occurs frequently, and pregnant women and their foetuses are particularly sensible to ID [25,26]. There are no first-trimester safety data, and IV supplementation of iron should therefore be restricted to the second and third trimester. In this latter context, a prospective randomized controlled trial with ferric carboxymaltose versus oral iron demonstrated a favorable safety profile [27]. At the same time, iv iron supplementation restored systemic maternal and foetal iron, and increased haemoglobin, sociability and vitality (according to SF-36) of the mothers in advanced gestation [27].

Hypophosphatemia

Different IV iron preparations induce hypophosphatemia, defined as serum phosphate levels <0.81 mmol/L [<2.5 mg/dL]. Severe hypophosphatemia (<0.32 mmol/L) may cause a broad spectrum of symptoms, such as fatigue, muscle weakness, muscle cramps, muscle spasms, myalgia, paraesthesia, seizures and arrhythmia [28]. Prolonged hypophosphatemia may also lead to abnormal osteoid mineralization and osteomalacia [29]. Although most patients with mild hypophosphatemia remain clinically asymptomatic [30], there is a need for long-term data on the effects of different repeatedly-administered preparations of IV iron on the bone and other outcomes. (Table 2) summarizes the prevalence of hypophosphatemia in response to commonly used IV iron formulations and its clinical relevance from randomized studies. Ferric carboxymaltose provokes hypophosphatemia more often compared to other formulations. This was illustrated in a study by Wolf *et al.* comparing the rate of hypophosphatemia when administering two doses of 750mg ferric carboxymaltose (at 1 week interval) versus a single administration of 1000mg iron isomaltoside. Ferric carboxymaltose-treated patients presented a higher percentage of hypophosphatemia (7.9% - 8.1% for ferric carboxymaltose vs 73.7% - 75.0% for iron isomaltoside),

Table 2: Administration and safety aspects of commonly used intravenous iron compounds.

	Administration		Safety		
Iron preparation	**Maximal infusion dose§**	**Minimal infusion time§**	**Hypophosphatemia**	**Hypersensitivity**	
			Prevalence in randomized studies*,#, [a] (mainly defined as serum phosphate <2 mg/dL)	**Reporting rate of severe hypersensitivity in large pharmacovigilance databases**,[c] [48]**	**Anti-dextran antibody reactions** [15,16][d]
Ferric carboxymaltose	20 mg/kg, max. 1000 mg	1000 mg during 15 min.	• Glaspy *et al.* 0% [69] • Macdougall *et al.* 0% [70] • Wolf *et al.* 75% [71][b]	0.18-1.47	No
Low molecular weight iron dextran	20 mg/kg	240-360 min.	• Glaspy *et al.* 0% [69] • Hussain et al. 0% [72]	0.22-2.8	Yes
Ferumoxytol	510 mg (recommended single dose)	510 during 15 min.	• Adkinson *et al.* 0.4 %[73] • Wolf et al. 0.9%[31]	NA	Yes
Ferric gluconate	125 mg	125 mg during 60 min.	No data	0.02-0.14	No
Iron(III)-isomaltoside 1000	20 mg/kg	1000 mg during >15 min.	• Derman *et al.*1.5 % [74] • Wolf *et al.* 8.1%[31][b]	0.0-7.94	Yes
Iron(III) sucrose	500 mg	500 mg during 210 min.	• Derman *et al.* 0%[74] • Glaspy *et al.* 40%[69]	0.03-0.2	No

*Randomized controlled studies, if possible with focus on hypophosphatemia as a predefined endpoint, were chosen to extract the prevalence of hypophosphatemia in order to gain insights from sources of the highest possible evidence level. The results of a recent meta-analysis [69] with focus on hypophosphatemia related to intravenous iron administration were also taken into consideration.

None of the studies reported clinically relevant symptoms and complications associated with hypophosphatemia [31,69,73-76].

**Reporting rates in large pharmacovigilance databases were chosen as a source to estimate the frequency of severe hypersensitivity to intravenous iron compounds, because this is a rare adverse reaction which cannot be easily captured in randomized controlled studies with patient numbers ranging from a few hundred to maximum a few thousand [48].

§ According to the Summary of Product Characteristics of respective iron preparations

[a] In a recent randomized controlled study, no hospitalizations and no particular treatments due to hypophosphatemia following administration of ferric carboxymaltose were documented [77]. Furthermore, analysis of pooled data from patients, who received ferric carboxymaltose in 45 interventional studies showed no correlation between measured serum phosphate levels and the occurrence of reported adverse events related to low phosphate [32].

[b] Severe hypophosphatemia defined as serum phosphate <1 mg/dL occurred in 11.3% of patients [71].

[c] Reports of severe hypersensitivity reactions included reports on anaphylactic reactions, anaphylactic shock, anaphylactoid reactions and anaphylactoid shock between 2010 and 2017 in 27 European countries [48]. Reporting rates were determined by dividing the number of reports of severe hypersensitivity reactions by the corresponding sales volume of 100 mg dose equivalents of iron for each type of intravenous iron. Reporting rates of severe hypersensitivity reactions per 100 000 defined daily doses of 100 mg dose equivalents are presented.

[d] The study includes low and high molecular weight iron dextran.

which increased further after administering the second dose [31]. However, this increase has, so far, not been associated with clinically relevant consequences. Mostly, hypophosphatemia has been transient and resolved within few weeks (~8-12 weeks) [32]. Nevertheless, post-marketing reports have identified patients with symptomatic hypophosphatemia requiring clinical intervention, including hypophosphatemic osteomalacia, following administration of ferric carboxymaltose in patients presenting risk factors (risk factors for developing severe hypophosphatemia are reported on Table 3) for developing low serum phosphate levels [33,34]. These incidents occurred in patients without renal impairment who had received repeated high doses of ferric carboxymaltose. These case reports suggest that serum phosphate values should be monitored in patients at risk for hypophosphatemia and in those who need repeated administration of IV iron. In addition, to allow restoration of phosphate levels clinicians should consider administering a high dose of IV ferric-carboxymaltose rather than shorten the interval of administration to 2 weeks or less [32]. The mechanism by which i.v. irons may cause hypophosphatemia may be related to the homeostasis of Fibroblast growth factor 23 (FGF23), a bone-derived hormone that lowers serum phosphate by promoting urinary phosphate excretion and through inhibition of calcitriol production. Treatment with i.v. iron preparations might shift the balance between FGF23 production and FGF23 cleavage by reducung FGF23 cleavage, which increases the levels of bioactive intact FGF23 leading to decreased serum phosphate levels [35].

In summary, in patients at risk for hypophosphataemia, repeated IV iron administration, especially with ferric- carboxymaltose, needs to be adapted to the disease of outset and its inherent risk for hypophosphataemia, other hypophosphataemia-inducing drugs and the time necessary to restitute iron stores.

Hypersensitivity Reaction

The most feared and life-threatening adverse reaction to IV iron administration is an anaphylactic shock. The proposed mechanism for this is an antibody-mediated dextran-induced anaphylaxis following repeated IV administration of dextran-containing products which react with pre-existing dextran-reactive antibodies [36]. Such reactions have limited the use of IV iron for many years as most humans have naturally-acquired anti-dextran antibodies [37,38]. The antibodies that seem to form in response to dextran are produced by widely-occurring intestinal bacteria and bacterial species that induce tooth decay [15,16,39-41]. More specifically, severe antibody-mediated dextran-induced anaphylaxis is an immune complex-mediated (type III) reaction that occurs when infused dextran molecules bind to endogenous dextran-reactive Immunoglobulin (Ig) G antibodies [42,43]. However, there are no

Table 3: Risk factors for developing hypersensitivity reactions or hypophosphatemia and relevant clinical symptoms.

Risk factors for hypersensitivity reaction*	Risk factors for hypophosphataemia**
• Known allergies, including drug allergies • History of severe asthma, eczema or another atopic allergy • Autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis	· Malabsorption of fat-soluble vitamins or phosphate (e.g. IBD · Concurrent or prior use of medications that affect proximal renal tubular function · Hyperparathyroidism · Vitamin D deficiency · Malnutrition (i.e. anorexia)
• Symptoms of Hypersensitivity	Symptoms of Hypophosphataemia
• Grade I : Skin symptoms and/or mild fever reaction • Grade II (measurable, but not life threatening): o Cardiovascular reaction (tachycardia, hypotension) o Gastrointestinal disturbance (nausea) o Respiratory • Grade III : Shock, life-threatening spams of smooth muscles (bronchi, uterus) • Grade IV: Cardiac and or respiratory arrest (78)	· Muscle weakness, cramps, spasm and myalgia · Paraesthesia · Seizures Arrhythmia (28). Prolonged hypophosphatemia : · Abnormal osteoid mineralization and osteomalacia

*According to summary of product characteristics of ferric carboxymaltose in Switzerland, November 2020
**According to summary of product characteristics of ferric carboxymaltose in the USA, February 2020

standardized tests to detect this type of reaction [44] and therefore this specific issue has not been evaluated broadly yet. Antibody-mediated dextran-induced anaphylaxis can potentially occur with any iron preparation containing dextran derivatives. More recently, studies have suggested other pathways that induce hypersensitivity in products of nanoparticle size via a non- immunologic pathway called Complement Activation-Related Pseudo-Allergy (CARPA) [45,46]. In this pathway, nanoparticles activate the complement system, leading to the formation of anaphylatoxins which then trigger liberation of histamine from mast cells and basophils.

Independent of the innate mechanisms underlying hypersensitivity reactions, it is their severity which determines their clinical relevance. (Table 2) summarizes the rate of severe hypersensitivity reactions upon commonly used IV iron formulations, based on large pharmacovigilance databases. Iron (III) sucrose, ferric gluconate and ferric carboxymaltose do not display reactions to anti-dextran antibodies *in vitro* [15,16] and seem to exhibit less severe hypersensitivity *in vivo* compared to other iv iron preparations [47,48].

Patients at Risk for Hypophosphatemia and Hypersensitivity

Clinicians should strive to identify patients at risk of developing hypophosphataemia or hypersensitivity. Following iv administration of ferric carboxymaltose, clinicians should instruct patients to seek medical advice if they experience worsening fatigue together with muscle pain or bone pain [49]. In addition, serum phosphate levels should be monitored in patients who receive consecutive multiple ferric carboxymaltose IV administrations at higher doses, and in those with existing risk factors for hypophosphatemia, as summarized in (Table 3). Prevention of this adverse effect should include sufficient vitamin D levels and supplementation, if required, in particular among patients with IBD [50]. As already mentioned above, clinicians should consider administering a high dose of ferric carboxymaltose rather than shortening intervals of administration to 2 weeks or less to allow restoration of phosphate levels in between applications of ferric carboxymaltose.

Similarly, clinicians should enquire about any factors that predispose patients to hypersensitivity, such as known allergies (including allergies to drugs), history of severe asthma, eczema or other atopic allergies, and autoimmune diseases, such as systemic lupus erythematosus and rheumatoid arthritis (Table 3). There is a lack of evidence showing that premedication with antiallergics may decrease the risk of hypersensitivity in such patients. Therefore, this approach is not advisable. Instead, iv iron mandates careful and systematic monitoring of vital parameters of the patient, from the beginning of the infusion until 30 minutes following the end of the infusion (Table 3) [51]. Finally, foetal bradycardia may occur following administration of parenteral irons. It is usually transient and a consequence of a hypersensitivity reaction in the mother. The unborn baby should be carefully monitored during intravenous administration of parenteral irons to pregnant women [51].

Attitudes and Real World Use of IV Iron

The most recently developed IV iron formulations have been on the market many years in several European countries. However, it is not fully clear whether IV iron is used appropriately in concordance with established evidence and guidelines in different indications. Ferric carboxymaltose and iron sucrose were developed and are produced in Switzerland. Here, clinicians have been using newer IV formulations for more than a decade. Furthermore, some pioneering studies have been carried out, such as the treatment of fatigue in ID without anaemia [52-54]. In Switzerland, the most frequent indication for either oral or IV iron therapy is ID without anaemia (59.4 and 74.7%, respectively) [55]. Severity of ID, presence of IBD [56] and advanced CKD [55] drive the choice between IV versus oral supplementation of iron [55]. Varcher *et al.* found that among patients treated for ID, 70% received oral iron, 14% IV iron preparations, and 16% received both [57]. The authors did not identify any distinguishable overutilization of IV iron [57]. According to the analysis of Biétry *et al.*, which was performed at a time when only iron (III) sucrose, ferric carboxymaltose and ferumoxytol were available, ferric carboxymaltose was the most commonly used preparation (86.3%). This could be due to its appearance in several recommendations and guidelines from this time period based on data from controlled clinical trials [56,58].

Physicians' use of iv iron replacement therapy in Switzerland follows to a high degree current European consensuses and guidelines on iron treatment in specific therapeutic areas, such as IBD [59], Chronic Heart Failure (CHF) [60] and CKD [58]; it also

follows Swiss recommendations on ID Anaemia (IDA) management during pregnancy and postpartum [61]. Additionally, general practitioners play an important role in diagnosing and treating ID in stable patients with CHF, non-dialyzed CKD patients, and pregnant women in coordination with their gynaecologist, whereas specialists manage patients with unstable disease [60]. This has been reflected in a recent consensus analysis among Swiss physician experts on the management of ID based on a survey using a Delphi method [62]. In line with the studies mentioned above [53,54] and data published by Meier *et al.* [55], Swiss physicians seem to reason about iv iron therapy with a high level of appropriateness not only for the management of IDA, but also for dealing with symptomatic ID without anaemia. According to this consensus analysis, iv iron can be considered if oral iron is not tolerated or not efficacious [62]. But, real world data about the level of monitoring and treatment of ID and IDA are lacking in Switzerland.

The 2021 European Society of Cardiology (ESC) Guidelines for the diagnosis and treatment of acute and chronic heart failure recommended that all patients with heart failure are periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT. The guidelines recommended that for the management of anaemia and iron deficiency in patients with heart failure, intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with iron deficiency to improve symptoms and reduce the risk of hospitalization [63,64].

A study from 2013 assessing routine management of IBD-associated ID and IDA in Europe showed a high prevalence of absolute ID (76%) and severe IDA (15%), suggesting insufficient monitoring and repletion of iron status in IBD with anaemia. The study also showed that management of IBD-associated IDA in Europe continues to rely on oral iron preparations (except in SE and CH). Although oral iron may be used in patients with mild anaemia, national (UK) and international (ECCO) guidelines stress the associated risk that oral iron may be poorly tolerated and may exacerbate symptoms [65].

Recently, Schiefke *et al* [66] presented an e-Delphi Survey conducted among 26 European experts on the optimal management of Gastrointestinal Bleeding (GIB)-IDA. The study suggests that experts in the field prescribe iron therapy based on clinical considerations, rather than laboratory test values or thresholds to treat. Experts recognize the importance and effectiveness of IV iron for the management of GIB-IDA, but consensus is lacking regarding its use as first-line therapy despite studies showing that it may be faster and more cost-effective than oral iron [60,67]. New guidance is therefore needed concerning optimal iron supplemental therapy of GIB-IDA, including recommendations on the use of IV iron formulations.

A European patient record study on diagnosis and treatment of Chemotherapy-Induced Anaemia (CIA) and ID including oncologists and/or haematologists from nine European countries demonstrated that management of anaemia and iron status in patients treated for CIA varies substantially across Europe. Iron status is only assessed in half of the patients. In contrast to clinical evidence, clinicians underutilise iron treatment and mainly prescribe oral iron supplementation. Better implementation of guidelines would minimize the use of blood transfusions [68].

All of these data suggest that reasoning about ID, assessment of ID and use of IV iron formulations in different conditions needs to be systematically developed further.

Authors' Contribution

All authors gave conceptual input for the content of the manuscript.

The manuscript was drafted by Pascal Juillerat, Jürg Stein *and* Edouard Battegay and then reviewed and modified by all members of the group.

All authors had access to references used, reviewed and approved the final manuscript and improved its scientific and clinical content.

Conflict of Interest

P. Juillerat and S. Restellini participated to advisory panels for Takeda, Janssen, Pierre Fabre (partner of Pharmacosmos in Switzerland), Vifor Pharma, but refused to receive honoraria.

A. Angelillo-Scherrer received consulting fees from Vifor Pharma.

M. H. Maillard received lecture fees and grants, and served as advisor for Vifor Pharma and for other companies not involved in iron supplementation.

P. Michetti received consulting fees from AstraZeneca, AbbVie, Ferring Pharmaceuticals, Janssen, MSD, Nestlé Health Sciences, Pfizer, Pierre Fabre (partner of Pharmacosmos in Switzerland), Takeda, UCB Pharma, and Vifor Pharma, lecture fees from Ferring Pharmaceuticals, Janssen, Hospira, MSD, Pfizer, Takeda, UCB Pharma, and Vifor Pharma and research grants from iQone.

A. Schoepfer received consulting fees and/or lecture fees and/or research grants from Adare Pharmaceuticals, Abbvie, Alfasigma, AstraZeneca, Celgene, Dr Falk Pharma, Janssen, MSD, Mylan, Norgine, Pfizer, Receptos, Regeneron, Takeda, UCB Pharma, and Vifor Pharma, Pierre Fabre (partner of Pharmacosmos in Switzerland).

E. Battegay has received consulting fees and speaker honoraria from Pierre Fabre (partner of Pharmacosmos in Switzerland) and from Roche Diagnostics International Ltd., honoraria, educational grants and study grants from Vifor Pharma and from other companies not involved in iron supplementation.

D. Surbek has received consulting fees and speaker honoraria from Vifor Pharma and from other companies not involved in iron supplementation.

G. Rogler has consulted to Abbvie, Augurix, BMS, Boehringer, Calypso, Celgene, FALK, Ferring, Fisher, Genentech, Gilead, Janssen, MSD, Novartis, Pfizer, Phadia, Roche, UCB, Takeda, Tillots, Vifor, Vital Solutions and Zeller. G. Rogler has received speaker's honoraria from Astra Zeneca, Abbvie, FALK, Janssen, MSD, Pfizer, Phadia, Takeda, Tillots, UCB, Vifor and Zeller. G. Rogler has received educational grants and research grants from Abbvie, Ardeypharm, Augurix, Calypso, FALK, Flamentera, MSD, Novartis, Pfizer, Roche, Takeda, Tillots, UCB, Vifor and Zeller.

E. Burri has received consultant and/or speaker fees from Abbvie, Amgen, Janssen, MSD, Norgine, Pfizer, Pierre Fabre (partner of

Pharmacosmos in Switzerland), Sandoz, Takeda, Vifor Pharma.

S. Vavricka has received consulting fees and unrestricted research grants from Abbott, Ferring Pharmaceuticals, MSD, Pfizer Inc, Janssen, Takeda, Tillotts, UCB, Vifor, and Falk Pharma GmbH.

L. Degen has no conflict of interest.

F. Seibold is medical advisor for Abbvie, MSD, Takeda, Vifor Pharma, Janssen, Amgen and Celgene.

L. Biedermann have received fees for consulting/advisory board and speaker fees from Abbvie, MSD, Vifor Pharma, Dr. Falk Pharma, Esocap, Calypso, Ferring, Pfizer, Shire, Takeda, Janssen, Ewopharma and Pharmacosmos.

J. Stein has received consulting fee or honorarium from Abbvie, Dr. Schär, Falk, Ferring, Fresenius Kabi, Immundiagnostik, Janssen, Medice, MSD, Pfizer, Pharmacosmos, Shire, Shield, Takeda, ThermoFisher, Vifor Pharma and is a board membership of Abbvie, Dr. Schär, Ferring, Fresenius Kabi, Immundiagnostik, Janssen, MSD, NPS, Pharmacosmos, Shield, Takeda, Vifor Pharma.

C. Mottet has received consulting/speaker fees from Vifor Pharma, Takeda, MSD Merck Sharp & Dohme, Abbvie AG, Mylan, UCB-Pharma SA, Janssen-Cilag AG.

References

1. Paschen HW. Conception and conception prevention (Neomalthusianism). Medizinische Klinik. 1949; 44: 97-102.
2. Auerbach M, Ballard H. Clinical use of intravenous iron: administration, efficacy, and safety. Hematology American Society of Hematology Education Program. 2010; 2010: 338-47.
3. Hadnagy C, Markus T, Szurkos I. Sideroblast content of the bone marrow at the end of pregnancy or 1st days of puerperium, respectively. Zentralblatt fur Gynakologie. 1977; 99: 1106-7.
4. Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmen J. Update on adverse drug events associated with parenteral iron. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2006; 21: 378-82.
5. Girelli D, Ugolini S, Busti F, Marchi G, Castagna A. Modern iron replacement therapy: clinical and pathophysiological insights. International journal of hematology. 2018; 107: 16-30.
6. Danielson BG. Structure, chemistry, and pharmacokinetics of intravenous iron agents. Journal of the American Society of Nephrology: JASN. 2004; 15: S93-8.
7. Neiser S, Rentsch D, Dippon U, Kappler A, Weidler PG, Gottlicher J, et al. Physico- chemical properties of the new generation IV iron preparations ferumoxytol, iron isomaltoside 1000 and ferric carboxymaltose. Biometals: an international journal on the role of metal ions in biology, biochemistry, and medicine. 2015; 28: 615-35.
8. Nikravesh N, Borchard G, Hofmann H, Philipp E, Fluhmann B, Wick P. Factors influencing safety and efficacy of intravenous iron-carbohydrate nanomedicines: From production to clinical practice. Nanomedicine: nanotechnology, biology, and medicine. 2020; 26: 102178.
9. Borchard G, Fluhmann B, Muhlebach S. Nanoparticle iron medicinal products - Requirements for approval of intended copies of non-biological complex drugs (NBCD) and the importance of clinical comparative studies. Regulatory toxicology and pharmacology: RTP. 2012; 64: 324-8.
10. Bhandari S. Intravenous Irons: From Basic Science to Clinical Practice. . Pharmaceuticals. 2018; 11: e82.
11. Adler M, Herrera-Gomez F, Martin-Garcia D, Gavid M, Alvarez FJ, Ochoa-Sangrador C. The Impact of Iron Supplementation for Treating Anemia in Patients with Chronic Kidney Disease: Results from Pairwise and Network Meta-Analyses of Randomized Controlled Trials. Pharmaceuticals. 2020; 13.
12. Aksan A, Isik H, Radeke HH, Dignass A, Stein J. Systematic review with network meta- analysis: comparative efficacy and tolerability of different intravenous iron formulations for the treatment of iron deficiency anaemia in patients with inflammatory bowel disease. Alimentary pharmacology & therapeutics. 2017; 45: 1303-18.
13. Pollock RF, Muduma G. A systematic literature review and indirect comparison of iron isomaltoside and ferric carboxymaltose in iron deficiency anemia after failure or intolerance of oral iron treatment. Expert review of hematology. 2019; 12: 129-36.
14. Rognoni C, Venturini S, Meregaglia M, Marmifero M, Tarricone R. Efficacy and Safety of Ferric Carboxymaltose and Other Formulations in Iron-Deficient Patients: A Systematic Review and Network Meta-analysis of Randomised Controlled Trials. Clinical drug investigation. 2016; 36: 177-94.
15. Neiser S, Wilhelm M, Schwarz K, Funk F, Geisser P, Burckhardt S. Assessment of dextran antigenicity of intravenous iron products by an immunodiffusion assay. Port J Nephrol Hypert. 2011; 25: 219-24.
16. Neiser S, Koskenkorva TS, Schwarz K, Wilhelm M, Burckhardt S. Assessment of Dextran Antigenicity of Intravenous Iron Preparations with Enzyme-Linked Immunosorbent Assay (ELISA). International journal of molecular sciences. 2016; 17.
17. Chandler G, Harchowal J, Macdougall IC. Intravenous iron sucrose: establishing a safe dose. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2001; 38: 988-91.
18. Ternes N, Scheiber-Mojdehkar B, Landgraf G, Goldenberg H, Sturm B. Iron availability and complex stability of iron hydroxyethyl starch and iron dextran a comparative in vitro study with liver cells and macrophages. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2007; 22: 2824- 30.
19. Zanen AL, Adriaansen HJ, van Bommel EF, Posthuma R, Th de Jong GM. 'Oversaturation' of transferrin after intravenous ferric gluconate (Ferrlecit(R)) in haemodialysis patients. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 1996; 11: 820-4.
20. Rampton D, Folkersen J, Fishbane S, Hedenus M, Howaldt S, Locatelli F, et al. Hypersensitivity reactions to intravenous iron: guidance for risk minimization and management. Haematologica. 2014; 99: 1671-6.
21. DeLoughery TG. Safety of Oral and Intravenous Iron. Acta haematologica. 2019; 142: 8- 12.
22. Avni T, Bieber A, Grossman A, Green H, Leibovici L, Gafter-Gvili A. The safety of intravenous iron preparations: systematic review and meta-analysis. Mayo Clinic proceedings. 2015; 90: 12-23.
23. Ramanathan G, Olynyk JK, Ferrari P. Diagnosing and preventing iron overload. Hemodialysis international International Symposium on Home Hemodialysis. 2017; 21: S58-S67.
24. Zager RA, Johnson AC, Hanson SY, Wasse H. Parenteral iron formulations: a comparative toxicologic analysis and mechanisms of cell injury. American journal of kidney diseases: the official journal of the National Kidney Foundation. 2002; 40: 90-103.
25. Means RT. Iron Deficiency and Iron Deficiency Anemia: Implications and Impact in Pregnancy, Fetal Development, and Early Childhood Parameters. Nutrients. 2020; 12.
26. Rahman SM, Siraj MS, Islam MR, Rahman A, Ekstrom EC. Association between maternal plasma ferritin level and infants' size at birth: a prospective cohort study in rural Bangladesh. Global health action. 2021; 14: 1870421.
27. Breymann C, Milman N, Mezzacasa A, Bernard R, Dudenhausen J, investigators F-A. Ferric carboxymaltose vs. oral iron in the treatment of pregnant women with iron deficiency anemia: an international, open-label, randomized controlled trial (FER-ASAP). Journal of perinatal medicine. 2017; 45: 443-53.
28. Bager P, Hvas CL, Dahlerup JF. Drug-specific hypophosphatemia and

hypersensitivity reactions following different intravenous iron infusions. British journal of clinical pharmacology. 2017; 83: 1118-25.

29. Zimmerman L, B. M. Osteomalacia: StatPearls Publishing; Treasure Island (FL). 2020.

30. Assadi F. Hypophosphatemia: an evidence-based problem-solving approach to clinical cases. Iranian journal of kidney diseases. 2010; 4: 195-201.

31. Wolf M, Rubin J, Achebe M, Econs MJ, Peacock M, Imel EA, et al. Effects of Iron Isomaltoside vs Ferric Carboxymaltose on Hypophosphatemia in Iron-Deficiency Anemia: Two Randomized Clinical Trials. Jama. 2020; 323: 432-43.

32. Rosano G, Schiefke I, Gohring UM, Fabien V, Bonassi S, Stein J. A Pooled Analysis of Serum Phosphate Measurements and Potential Hypophosphataemia Events in 45 Interventional Trials with Ferric Carboxymaltose. Journal of clinical medicine. 2020; 9.

33. Mani LY, Nseir G, Venetz JP, Pascual M. Severe hypophosphatemia after intravenous administration of iron carboxymaltose in a stable renal transplant recipient. Transplantation. 2010; 90: 804-5.

34. Fierz YC, Kenmeni R, Gonthier A, Lier F, Pralong F, Coti Bertrand P. Severe and prolonged hypophosphatemia after intravenous iron administration in a malnourished patient. European journal of clinical nutrition. 2014; 68: 531-3.

35. Frazier R, Hodakowski A, Cai X, Lee J, Zakarija A, Stein B, et al. Effects of ferric carboxymaltose on markers of mineral and bone metabolism: A single-center prospective observational study of women with iron deficiency. Bone. 2020; 141: 115559.

36. Zinderman CE, Landow L, Wise RP. Anaphylactoid reactions to Dextran 40 and 70: reports to the United States Food and Drug Administration, 1969 to 2004. Journal of vascular surgery. 2006; 43: 1004-9.

37. Hamstra RD, Block MH, Schocket AL. Intravenous iron dextran in clinical medicine. Jama. 1980; 243: 1726-31.

38. Fishbane S, Ungureanu VD, Maesaka JK, Kaupke CJ, Lim V, Wish J. The safety of intravenous iron dextran in hemodialysis patients. American journal of kidney diseases: the official journal of the National Kidney Foundation. 1996; 28: 529-34.

39. Richter AW, Hedin HI. Dextran hypersensitivity. Immunology today. 1982; 3: 132-8.

40. Hedin H, Richter W. Pathomechanisms of dextran-induced anaphylactoid/anaphylactic reactions in man. International archives of allergy and applied immunology. 1982; 68: 122-6.

41. Assessment report for: Iron containing intravenous (IV) medicinal products, 13 September 2013, EMA/549569/2013, Procedure under Article 31 of Directive 2001/83/EC, Procedure number: EMEA/H/A-31/1322 4.

42. Kraft D, Hedin H, Richter W, Scheiner O, Rumpold H, Devey ME. Immunoglobulin class and subclass distribution of dextran-reactive antibodies in human reactors and non reactors to clinical dextran. Allergy. 1982; 37: 481-9.

43. Novey HS, Pahl M, Haydik I, Vaziri ND. Immunologic studies of anaphylaxis to iron dextran in patients on renal dialysis. Annals of allergy. 1994; 72: 224-8.

44. Bircher AJ, Auerbach M. Hypersensitivity from intravenous iron products. Immunology and allergy clinics of North America. 2014; 34: 707-23, x-xi.

45. Macdougall IC, Vernon K. Complement Activation-Related Pseudo-Allergy: A Fresh Look at Hypersensitivity Reactions to Intravenous Iron. American journal of nephrology. 2017; 45: 60-2.

46. Verhoef JJF, de Groot AM, van Moorsel M, Ritsema J, Beztsinna N, Maas C, et al. Iron nanomedicines induce Toll-like receptor activation, cytokine production and complement activation. Biomaterials. 2017; 119: 68-77.

47. Ehlken B, Nathell L, Gohlke A, Bocuk D, Toussi M, Wohlfeil S. Evaluation of the Reported Rates of Severe Hypersensitivity Reactions Associated with Ferric Carboxymaltose and Iron (III) Isomaltoside 1000 in Europe Based on Data from EudraVigilance and VigiBase between 2014 and 2017. Drug safety. 2019; 42: 463-71.

48. Nathell L, Gohlke A, Wohlfeil S. Reported Severe Hypersensitivity Reactions after Intravenous Iron Administration in the European Economic Area (EEA) Before and After Implementation of Risk Minimization Measures. Drug safety. 2020; 43: 35-43.

49. Summary of product characteristics of ferric carboxymaltose in UK, October 2020 https: //www.medicines.org.uk

50. Madanchi M, Fagagnini S, Fournier N, Biedermann L, Zeitz J, Battegay E, et al. The Relevance of Vitamin and Iron Deficiency in Patients with Inflammatory Bowel Diseases in Patients of the Swiss IBD Cohort. Inflammatory bowel diseases. 2018; 24: 1768-79.

51. Summary of Product Characteristics of Ferinject: www.swissmedicinfo.ch

52. Favrat B, Balck K, Breymann C, Hedenus M, Keller T, Mezzacasa A, et al. Evaluation of a single dose of ferric carboxymaltose in fatigued, iron-deficient women--PREFER a randomized, placebo-controlled study. PloS one. 2014; 9: e94217.

53. Krayenbuehl PA, Battegay E, Breymann C, Furrer J, Schulthess G. Intravenous iron for the treatment of fatigue in nonanemic, premenopausal women with low serum ferritin concentration. Blood. 2011; 118: 3222-7.

54. Verdon F, Burnand B, Stubi CL, Bonard C, Graff M, Michaud A, et al. Iron supplementation for unexplained fatigue in non-anaemic women: double blind randomised placebo controlled trial. Bmj. 2003; 326: 1124.

55. Meier R, Keizer E, Rosemann T, Markun S. Indications and associated factors for prescribing intravenous iron supplementation in Swiss general practice: a retrospective observational study. Swiss medical weekly. 2019; 149: w20127.

56. Voegtlin M, Vavricka SR, Schoepfer AM, Straumann A, Voegtlin J, Rogler G, et al. Prevalence of anaemia in inflammatory bowel disease in Switzerland: a cross-sectional study in patients from private practices and university hospitals. Journal of Crohn's & colitis. 2010; 4: 642-8.

57. Varcher M, Zisimopoulou S, Braillard O, Favrat B, Junod Perron N. Iron deficiency intravenous substitution in a Swiss academic primary care division: analysis of practices. International journal of general medicine. 2016; 9: 221-7.

58. Locatelli F, Barany P, Covic A, De Francisco A, Del Vecchio L, Goldsmith D, et al. Kidney Disease: Improving Global Outcomes guidelines on anaemia management in chronic kidney disease: a European Renal Best Practice position statement. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2013; 28: 1346-59.

59. Dignass AU, Gasche C, Bettenworth D, Birgegard G, Danese S, Gisbert JP, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. Journal of Crohn's & colitis. 2015; 9: 211-22.

60. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2016; 7: 2129-200.

61. Breymann C, Honegger C, Hosli I, Surbek D. Diagnosis and treatment of iron-deficiency anaemia in pregnancy and postpartum. Archives of gynecology and obstetrics. 2017; 296: 1229- 34.

62. Nowak A, Angelillo-Scherrer A, Betticher D, Dickenmann M, Guessous I, Juillerat P, et al. Swiss Delphi study on iron deficiency. Swiss medical weekly. 2019; 149: w20097.

63. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. Corrigendum to: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. European heart journal. 2021; 42: 4901.

64. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Bohm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. European heart journal. 2021; 42: 3599-726.

65. Stein J, Bager P, Befrits R, Gasche C, Gudehus M, Lerebours E, et al. Anaemia management in patients with inflammatory bowel disease: routine practice across nine European countries. European journal of gastroenterology & hepatology. 2013; 25: 1456-63.

66. Schiefke I, Stein J, Wehkamp J, Hawkey C, Wendt R, Clark P, et al. Delphi Study on the Management of Iron Deficiency Anemia in Patients with Gastrointestinal Bleeding. UEG Journal. 2016; 4: A485.

67. Lam CSP, Doehner W, Comin-Colet J, Group IC. Iron deficiency in chronic heart failure: case-based practical guidance. ESC heart failure. 2018; 5: 764-71.

68. Ludwig H, Aapro M, Bokemeyer C, Glaspy J, Hedenus M, Littlewood TJ, et al. A European patient record study on diagnosis and treatment of chemotherapy-induced anaemia. Supportive care in cancer: official journal of the Multinational Association of Supportive Care in Cancer. 2014; 22: 2197-206.

69. Glaspy JA, Lim-Watson MZ, Libre MA, Karkare SS, Hadker N, Bajic-Lucas A, et al. Hypophosphatemia Associated with Intravenous Iron Therapies for Iron Deficiency Anemia: A Systematic Literature Review. Therapeutics and clinical risk management. 2020; 16: 245-59.

70. Macdougall IC, White C, Anker SD, Bhandari S, Farrington K, Kalra PA, et al. Randomized Trial Comparing Proactive, High-Dose versus Reactive, Low-Dose Intravenous Iron Supplementation in Hemodialysis (PIVOTAL): Study Design and Baseline Data. American journal of nephrology. 2018; 48: 260-8.

71. Wolf M, Chertow GM, Macdougall IC, Kaper R, Krop J, Strauss W. Randomized trial of intravenous iron-induced hypophosphatemia. JCI insight. 2018; 3.

72. Hussain I, Bhoyroo J, Butcher A, Koch TA, He A, Bregman DB. Direct Comparison of the Safety and Efficacy of Ferric Carboxymaltose versus Iron Dextran in Patients with Iron Deficiency Anemia. Anemia. 2013; 2013: 169107.

73. Adkinson NF, Strauss WE, Macdougall IC, Bernard KE, Auerbach M, Kaper RF, et al. Comparative safety of intravenous ferumoxytol versus ferric carboxymaltose in iron deficiency anemia: A randomized trial. American journal of hematology. 2018; 93: 683-90.

74. Derman R, Roman E, Modiano MR, Achebe MM, Thomsen LL, Auerbach M. A randomized trial of iron isomaltoside versus iron sucrose in patients with iron deficiency anemia. American journal of hematology. 2017; 92: 286-91.

75. Evstatiev R, Marteau P, Iqbal T, Khalif IL, Stein J, Bokemeyer B, et al. FERGIcor, a randomized controlled trial on ferric carboxymaltose for iron deficiency anemia in inflammatory bowel disease. Gastroenterology. 2011; 141: 846-53 e1-2.

76. Mahey R, Kriplani A, Mogili KD, Bhatla N, Kachhawa G, Saxena R. Randomized controlled trial comparing ferric carboxymaltose and iron sucrose for treatment of iron deficiency anemia due to abnormal uterine bleeding. International journal of gynaecology and obstetrics: the official organ of the International Federation of Gynaecology and Obstetrics. 2016; 133: 43-8.

77. Wolf M, Koch TA, Bregman DB. Effects of iron deficiency anemia and its treatment on fibroblast growth factor 23 and phosphate homeostasis in women. Journal of bone and mineral research: the official journal of the American Society for Bone and Mineral Research. 2013; 28: 1793-803.

78. Ring J, Messmer K. Incidence and severity of anaphylactoid reactions to colloid volume substitutes. Lancet. 1977; 1: 466-9.