

Iron deficiency anemia – new possibilities of iron supplementation in various clinical conditions

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Iron deficiency anemia (IDA) treatment is done to eliminate the causes of iron deficiency, iron supplementation, and rarely red blood cell transfusion. Divalent iron salts are the first line of oral treatment, but their use lead to frequent gastrointestinal adverse reactions. Iron is administered intravenously in the event of contraindications, intolerance, or inefficiency of oral therapy, but the parenteral route of drug delivery is not easily accepted by the patients. Intravenous preparations for single administration of a large dose of iron have a good therapy safety profile, but are more expensive than oral and are usually administered in a hospital setting. The availability of new iron compounds: sucrosomial iron, ferric citrate complexes, and ferric maltol widen the possibilities of IDA therapy and enable the better selection of iron preparations in various clinical situations. The innovative structure of sucrosomial iron leads to absorption in different ways (through endocytosis, the paracellular pathway, M cells of Peyer's patches), ensures high bioavailability, and good tolerance of therapy. Ferric citrate, in addition to iron supplementation, reduces phosphate levels, and is beneficial to chronic kidney disease. Ferric maltol is currently being studied for IDA treatment with various comorbidities. Some studies indicate that new iron formulas may be used where intravenous intake has been recommended so far. So, we can expect treatment with iron nanoparticles and drugs that affect the intestinal microflora in the future. The paper presents current knowledge about new iron preparations that are already available in everyday practice, but also those that are at various stages of pre-clinical and clinical studies.

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Keywords:

iron deficiency anemia, sucrosomial iron, iron maltol, iron citrate, iron nanocompounds

Introduction

Iron deficiency anemia (IDA) is one of the most important common types of anemia worldwide, but its prevalence varies with latitude, country socioeconomic conditions, and patient age. It is estimated that IDA affects 1.24 billion people worldwide, most often children under the age of 5 and women of childbearing age. Globally, approximately 90% anemia cases in young children are caused by iron deficiency and infections. Deficiency anemia, including IDA and anemia in chronic kidney disease (CKD), are the two most common types of anemia in the elderly in the world [1]. It is estimated that in developed countries, IDA accounts for approximately 12–25% of anemia cases in patients over 60 years of age, who are not hospitalized [2–5].

The etiology of iron deficiency anemia varies among age groups. Increased need of iron requirements and dietary deficiencies are the most common causes of IDA during pregnancy, breastfeeding, and childhood. Blood loss during menstruation is the leading cause of iron deficiency in menstruating women, and iron malabsorption can occur at any age for a variety of reasons. One of the most common causes of iron deficiency, especially in the elderly, is bleeding, particularly from the gastrointestinal tract. Pharmacotherapy which commonly uses non-steroidal anti-inflammatory drugs, anticoagulants, antiplatelet drugs, or proton pump inhibitors thereby increasing the risk of IDA. The etiology of iron deficiency also includes blood loss caused by medical procedures

and surgery, especially in the elderly. Iron deficiency may appear in the course of many diseases, e.g., inflammatory bowel disease, chronic circulatory failure, chronic kidney disease, cancer, rheumatoid arthritis, and obesity. A rare, genetically determined form of IDA is iron-refractory iron deficiency anemia (IRIDA) [6–10]. Hepcidin, which is a direct inhibitor of ferroportin, plays a central role in the pathogenesis of iron metabolism disorders. Up-regulation of hepcidin inhibits iron transport from enterocytes and macrophages result in decreased iron availability for erythropoiesis. Hepcidin expression is inhibited by iron deficiency, erythropoietin, and hypoxia. Contrarily, increased iron intake and inflammatory response increase the expression of hepcidin. Both the deficiency and resistance to erythropoietin contribute to the pathogenesis of anemia. A detailed discussion of the pathogenesis of IDA is beyond the scope of this article and can be found in previously published papers [9, 10, 11].

Diagnostics

Coexistence of iron deficiency and inflammatory response give rise to some difficulties in the diagnosis and treatment of IDA. Therefore, practically absolute iron deficiency (ID) and functional iron deficiency (FID) is determined for diagnosis. ID indicates a reduction in total iron stores in the body and the need for iron supplementation. In most patients, ID is recognized at serum ferritin levels <30 ng/mL. The same

ferritin levels define iron deficiency anemia, with concentrations typically below 10–12 ng/mL [6]. There are no common criteria for identifying IDA in the literature. According to a review published in 2020 in the European Journal of Hematology, ferritin concentrations <12–50 ng/mL and transferrin saturation (TSAT) <16% were given as diagnostic criteria for IDA [7]. In turn, the publication of the American Society of Hematology in December 2019 proposed to diagnose IDA with ferritin <20 ng/mL and TSAT <20% [10]. For some diseases, the need for iron treatment is defined differently. In cancer, ID is diagnosed at a ferritin concentration of <100 ng/mL [12] while in chronic kidney disease, iron supplementation is recommended at ferritin level \leq 500 ng/mL and TSAT \leq 30% [13]. However, intravenous iron therapy can be used in symptomatic heart failure when ferritin is <100 ng/mL or <300 ng/mL and TSAT <20% [14, 15].

FID is a state of unavailability of sufficient iron for erythropoiesis despite adequate reserves in the body and occurs in anemia of chronic disease (ACD) or in the course of IRIDA [10]. FID in the course of IRIDA is diagnosed when serum iron concentration is decreased and TSAT <10%, but at different ferritin concentrations [7]. ACD with iron deficiency is diagnosed in patients with increased levels of inflammatory response markers and TSAT <20%, while serum ferritin concentrations are 30–100 ng/mL [16,17] or at 20–100 ng/mL according to some authors. [10]. The diagnosis of ACD is confirmed by the concentration of ferritin >100 ng/mL and TSAT <20% [7, 10, 18]. Serum soluble transferrin receptor (sTfR) concentration, sTfR to log ferritin concentration ratio (sTfR/log sF), and serum hepcidin concentration may be helpful in differential diagnosis of ID and ACD. In the course of ACD, sTfR is normal, hepcidin concentration is increased, and sTfR/log sF is below <1 [18, 19, 20]. During iron deficiency in the course of ACD, sTfR/log sF is >2, while the concentration of hepcidin varies [18, 20]. Currently hepcidin concentration is not used in routine practice mostly due to the lack of standardized reference values. But, hepcidin concentration may become one of the important parameters in the diagnosis and treatment of iron disorders in the future. In IDA, hepcidin levels might play an important role in deciding on the route of iron supplementation: low levels indicate the possibility of oral supplementation, and high levels indicate the need for parenteral treatment.

Treatment of IDA

In IDA, it is important to diagnose and eliminate the cause of iron deficiency while simultaneously maintaining dietary management and iron supplementation. The first line of treatment in patients without contraindications is oral supplementation with divalent iron – especially iron sulfate (i.e., salts of divalent iron (Fe^{2+})). The second line of treatment includes trivalent iron (Fe^{3+}) preparations, e.g., complexed with sugars or protein succinate [21]. Preparations containing divalent iron, e.g., iron sulfate and gluconate or iron fumarate are characterized by better bioavailability compared to trivalent iron preparations. Drugs containing divalent iron salts are relatively cheap, but should not be taken during meals as their use is associated with frequent gastrointestinal tract side effects [22]. Up to 70% of patients treated with oral iron preparations report symptoms

such as: abdominal pain, nausea, and constipation, that often lead to discontinuation of the treatment [23]. Gastrointestinal side effects result from the instability of bivalent iron, which is converted into trivalent iron by oxidation process resulting in the formation of reactive oxygen species (ROS). ROS not only damage enterocytes but also induce systemic inflammation and tissue damage. Moreover, only 10–20% of iron in the digestive tract is absorbed, and most of it remains available to intestinal microorganisms, which in turn alters the intestinal microflora and can result in intestinal inflammation and possibly neoplastic transformation [24, 25]. Due to lower absorption, the use of oral preparations of trivalent iron is recommended in the second-line of treatment in patients with intolerance to bivalent iron preparations. Parenteral iron supply is reserved for the cases having significant intolerance to oral preparations, exacerbation of inflammatory bowel disease (IBD), significant iron loss, the need to quickly restore iron stores, impaired iron absorption, active inflammation, iron deficiency in the course of chronic kidney disease especially when treated with erythropoietin, and in patients on dialysis. Preparations for parenteral administration with trivalent iron may contain iron sucrose complex, sodium-iron gluconate complex, iron dextran, as well as iron, sorbitol and citrate complex. The use of parenteral iron preparations, especially iron dextran, is associated with some risk of hypersensitivity reactions, including severe cases [26]. Intravenous iron supply causes faster and more effective restoration of iron resources in the body and also under conditions of inflammation, but involves a risk of iron overload. For several years, parenteral iron preparations for a single administration of a large dose of iron have been available in the form of: iron III hydroxide and carboxymaltose complex (Ferinject) [27] and iron isomaltoside 1000 III (Monover) [28]. It is already proved that their effectiveness is very good and has low risk for side effects, but they are expensive and are not used in outpatient care in Poland.

Red blood cell (RBC) transfusion is only used in patients with severe anemia and hemodynamic instability, signs of organ hypoxia (especially coronary symptoms), and active bleeding. RBC transfusion is associated with a number of well-documented serious immune and non-immunological adverse events mentioned above [29].

So, it may be concluded that though there are many oral iron preparations available at present, their use may be limited due to side effects, intolerance, or contraindications. On the other hand, intravenous iron preparations are not preferred by patients as they are more expensive and usually require hospitalization. Therefore, the aim of this study is to discuss new, original preparations for oral iron supplementation: sucrosomial iron, iron citrate complexes, or iron maltol complexes (Tab. I), their efficacy and applications in various clinical situations.

New iron preparations

Sucrosomial iron

Currently, a new preparation of sucrosomial iron, which is a patented one, is available, i.e., Sideral RM (SRM, PharmaNutra Spa), in which iron pyrophosphate (Fe^{3+}) is protected by a double

Table 1. Efficacy and safety of novel iron agents in a different clinical setting

Novel agents and references	Study population with anemia	Study type and duration	Dosage of agents	Results	SAEs	AEs
Sucrosomial Iron Pisani et al. [38]	NDD-CKD n = 99	RCT 3 months	SI 30 mg/d p.o. vs. FG IV (125 mg/week; 1000 mg total dose)	Increases Hb levels, ferritin in both groups; but stable after discontinuation in FG group	No in both group	Fever AEs in SI than FG group ⁴
Sucrosomial Iron Mafodda et al. [39]	Solid tumor n = 64	RCT pilot 2 months	SI (30 mg/d) vs. FG IV (125 mg/week) plus darbepoetin in both groups	No difference in the Hb response between 2 groups ¹	No differences between the groups	No differences between the groups
Sucrosomial Iron Abbati et al. [40]	Inflammatory bowel disease n = 30	Prospective 3 months	SI (30 mg/d)	Iron parameters, serum hepcidin improved significantly, Hb increased in 86% of patients ²	1 patients (3,33%) worsenieng of UC	80% of patients ⁵
Sucrosomial Iron Elli et al. [41]	Celiac disease n = 43	Prospective 3 months	SI (30 mg/d) vs. FS (105 mg EI/d)	Increase Hb levels compared to baseline (+10.1% and +16.2% for sucrosomial and sulfate groups, respectively)	No in both group	No differences between groups, SI group a lower severity of abdominal symptoms
Sucrosomial Iron Renso et al. [43]	Lympho-proliferative diseases n = 21	Retrospective 4–8 weeks	SI (30 mg/d) plus darbopoetin	Increase of Hb of 1.73 g/dL during 8 weeks, 8 patients required RBC transfusion	No in both group	4% any grade
Sucrosomial Iron Ciudin et al. [44]	Bariatric surgery n = 40	Case-control 3 months	SI (28 mg/d) vs. IRS (300 mg IV)	No differences in ferritin, TSaT, Hb, before and after treatment with SI	No in both group	No in both group
Ferric citrate Block et al. [48]	CKD stages 3-5 n = 249	RCT 12 weeks	FC (n = 117) vs. placebo (n = 115)	Increases Hb, repletes iron stores, reduces levels of serum phosphate, urinary phosphate excretion, and FGF-23	8% in FC vs. 12% placebo group ³	Incidence and severity of AEs similar between FC vs. placebo groups ⁶
Ferric citrate Fishbane et al. [49]	NDD-CKD n = 99	RCT phase 3 16 weeks	FC (starting dose 3 x 210 mg EI/d) vs. placebo	52.1% of FC group vs. 19.1% placebo increase in Hb \geq 1.0 g/dL	Similar rates (12.0% FC vs. 11.2% placebo groups)	75.3% of FC vs 61.7% of placebo-treat.e.d patients ⁷
Ferric citrate Chertof et al. [58]	NDD-CKD n = 385	Two RCT phase 2 (12 weeks) and phase 3 (16 weeks)	FC (starting dose 3 x 210 mg EI/d) vs. placebo	Correction of IDA (Hb \geq 10 g/L) and phosphatemia	10.5% FC vs. 11.2% placebo group. 2 patients (1.1%) died in each group	Gastrointestinal AEs ⁸ higher rates than in placebo group
Ferric maltol Gasche et al. [63]	Inflammatory bowel disease n = 128	Multicenter RCT phase 3 12 weeks	FM (60 mg/d) vs. placebo	Improvements in Hb in FM group, normalization of Hb in 2/3 of patients	SAEs unrelated to study	58% in FM group vs. 72% in placebo group ⁹
Ferric maltol Schmidt et al. [64]	Inflammatory bowel disease n = 111	RCT (first 12 weeks) open-label ferric maltol for 52 weeks	FM (30 mg/d) vs. placebo	Normalization of Hb in \geq 80% of patients from weeks 20–64	11 SAEs during 64 weeks ¹¹ , no deaths	24% patients of FM group ¹⁰

AEs – adverse events; CKD - chronic kidney disease; d – day; EI- elemental iron; FG - ferrous gluconate; Hb- hemoglobin; FS - ferrous sulfate; FM – ferric maltol; IRS – iron sucrose; NDD – nondialysis-dependent; RCT – randomized controlled trial; SAEs – serious adverse events; SI – sucrosomial iron; tabl – tablets; TSAT – transferrin saturation; UC – ulcerative colitis; VI – intravenous injection; ¹ – Hb from 9.4 to 12.7 g/dL in SI group and from 9.2 to 12.9 g/dL in FG; ² – Hb from 11.67 to 12.37 g/dl; ³ – SAEs in FC group: atrial fibrillation, gut complications, procedural complications, hypoglycemia; ⁴ – SAEs in SRI group: constipation 5%, diarrhea 5%, in FG group: headache 18%, hypotension 12%, infusion site reaction 12%; ⁵ – gastrointestinal adverse events: 30% of patients, other AEs (the most common: headache, sore throat, infection) 50% of patients; ⁶ – Most common AEs: diarrhea 20.5% vs. 16.4% and constipation 18.8% vs. 12.9% respectively; ⁷ – gastrointestinal AEs were the most frequent 49.5% FM vs. 27.7% placebo group; ⁸ – gastrointestinal AEs: diarrhea, constipation, nausea discolored feces; ⁹ – mainly gastrointestinal AEs FM vs. placebo: abdominal pain (13.3% vs. 11.7%, respectively), diarrhea (8.3% vs. 10.0%) and constipation (8.3% vs. 1.7%), naso-pharyngitis in 6.7% of FM vs. 11.7% of placebo group, ¹⁰ – AEs: abdominal pain 7% patients, constipation 5%, flatulence 5% and diarrhea 3%, ¹¹ – SAEs: severe abdominal pain, worsened ulcerative colitis, herpes zoster, peritonitis, hernia, cholesteatoma removal, rectal haemorrhage

layer of phospholipids and a sucrosomial shell called sucrester. The phospholipid layer is produced mainly from sunflower lecithin, while sucrester is a surfactant resulting from the esterification of fatty acids with sucrose. Other ingredients, such as tricalcium phosphate and starch, stabilize the molecule [30, 31]. The innovative formula allows iron absorption through various routes in the small intestine. A significant part of SRM is absorbed through endocytosis of the microcapsule by enterocytes of the intestinal epithelium. Further, absorption in part occurs by paracellular transport, and partly by specialized microfold cells of Peyer's patches (M cells) [31, 32, 33]. The results obtained in *in vitro* studies and animal models indicate that iron in the SRM formula is protected against reduction to divalent iron on the enterocyte surface and absorption is probably independent of divalent metal transporter 1 (DMT1) [30]. The specific route of absorption by M cells, a characteristic for sucrosomial iron, initially causes the iron to enter the lymphatic system instead of entering the blood. Different absorption routes and partial bypassing of the portal system and the liver is probably responsible for the high bioavailability of this preparation. Sucrester forms a protective layer that prevents iron from being released in the stomach, and allows release in the small intestine. In addition, iron is reduced to divalent ions on the surface of enterocytes only to a small extent, the amount of unabsorbed iron on the intestinal epithelium is reduced, and there are fewer gastrointestinal tract side effects [31, 32].

A number of *in vitro* and *in vivo* tests performed in healthy laboratory animals indicate better bioavailability of sucrosomial iron compared to other iron formulas, also other preparations of iron pyrophosphate or iron sulfate [30, 31, 34]. *In vivo* studies performed in animals with anemia, a greater improvement was observed in iron metabolism parameters and Hb metabolism with the use of SRM versus iron sulfate or iron dextran [35, 36]. Additionally, when mice with IDA treated with SRM, no increase in inflammatory parameters or a significant increase in hepcidin transcription was shown. Iron sulfate used in this study at the same doses caused a significant increase in hepcidin mRNA in hepatocytes and in serum hepcidin concentration. Iron sulfate induced the expression of various inflammatory markers [suppressor of cytokine signaling 3 (Socs3), serum amyloid A 1 (Saa1), interleukin-6 (IL6), and C-reactive protein (CRP)], which was not observed with SRM [35].

The safety and good tolerance of sucrosomial iron have been confirmed in patients with various diseases, including CKD [37, 38], tumors [39], inflammatory bowel diseases [40], and celiac disease [41]. The recommended daily dose for the treatment of IDA used in most studies is 30 mg/day of sucrosomial iron. The use of SRM together with darbepoetin alfa gives a similar increase in Hb in cancer patients with anemia associated with chemotherapy, with the use of intravenous preparations having better tolerance and without the risk of side effects typical of parenteral iron therapy [39]. Other studies on the use of SRM in oncohematology include a retrospective analysis of therapy cost in refractory anemia [42] and the effectiveness of anemia treatment in the course of lymphoproliferative diseases [43]. In patients after bariatric surgery, it was concluded that SRM can replace the intravenous iron supply [44]. Campanella and coauthors had similar observations for IDA patients, as SRM was shown to be effective and well-tolerated in situations where parenteral therapy

was indicated [45]. Some authors indicate the economic benefits of sucrosomial iron, especially when compared to parenteral therapy [42, 46]. However, most studies have been carried out in small groups of patients (20–90) and there have been only a few high-quality studies, so further studies are needed to completely evaluate the effects of SRM in different disease entities. Recruitment is currently underway for clinical trials involving sucrosomial iron in patients with anemia prior to cardiac surgery (ClinicalTrials.gov: NCT03560687), undergoing knee or hip orthopedic surgery (ClinicalTrials.gov: NCT04078880), and in patients with heart failure – including an efficacy comparison of various oral and intravenous iron preparations (ClinicalTrials.gov: NCT03833336). The use of SRM in heart failure would be an attractive alternative to intravenous treatment in patients who do not require hospitalization.

Iron citrate

Iron citrate was originally used as a non-calcium formulation to reduce the phosphate pool in patients with CKD. During treatment, it was observed that it has the ability to improve Hb parameters in patients with anemia [47]. In a double-blind, placebo-controlled, randomized study of patients with IDA and CKD stages 3–5, iron citrate has been found to improve iron metabolism parameters, increase Hb levels, reduce serum phosphate levels, and decrease fibroblast growth factor 23 (FGF23) levels over 12 weeks of treatment [48]. Fishbane et al. [49] demonstrated the efficacy, safety, and good tolerability of iron citrate treatment in non-dialyzed patients. Iron citrate can be used in non-dialyzed patients with CKD and IDA based on current recommendations, but further studies are needed to determine the role of iron citrate in dialyzed patients [50]. Iron citrate has also been studied in patients with CKD and heart failure (HF). Based on the results of phase 2 and 3 studies, it is found that HF did not affect the improvement in Hb, iron, or phosphate, but patients with HF reported more side effects [51]. The role of iron citrate in patients with CKD and HF requires further research.

Auryxia (Keryx Biopharmaceuticals, Inc.) is one of the oral iron citrate formulations approved for the treatment of hyperphosphatemia and IDA in CKD. Auryxia is distinguished by the fact that it is a solid mixture of iron citrate coordination complexes (FCCC) with a defined molar ratio of iron (Fe^{3+}) to citrate anions. X-ray crystallography reveals that these complexes are mono-, di-, tri- and nanonuclears with 2–9 iron atoms present in the complex, predominantly with dinuclears. The presence of various complexes increases the solubility and availability of iron under various pH conditions. Oligomeric complexes dominate under low pH conditions, while monomeric complexes at high pH [50, 52]. It is believed that the ability to form oligomeric complexes at low pH, i.e., in the stomach, contributes to the formation of insoluble complexes with phosphate ions and thus enables capture and removal of dietary phosphate from the body. The structure of iron-citrate complexes prevents the hydrolysis of ferric ions, which could lead to the formation of insoluble compounds. In addition, the iron in this preparation is weakly oxidized leading to the reduction in the formation of free oxygen radicals and lowers the risk of damage to the cells of the gastrointestinal mucosa. This reduces the likelihood of side effects [53]. The absorption of iron from Auryxia is mainly via

the known enterocytic absorption pathway. It is believed that other possible iron citrate absorption pathways include an extracellular pathway [54] and the mechanisms involving intestinal microflora [55]. Iron citrate complexes have been shown to capture and reduce phosphate and FGF23 levels in both dialyzed and non-dialyzed CKD patients [53]. As phosphates [56] and FGF23 [57] are independent factors of cardiovascular complications in patients with CKD, this preparation might be particularly beneficial in patients with CKD anemia. However, more research is needed to investigate whether the reduction of these parameters by Auryxia actually translates into cardiovascular risk reduction. Similarly to other iron preparations, gastrointestinal symptoms were the main adverse reactions in the analysis of two randomized phase 2 and 3 clinical trials of Auryxia in non-dialyzed patients with CKD. Serious adverse events that occurred in 20 patients treated with Auryxia compared to the group of 21 placebo patients include: cardiovascular disorders (3.7% vs. 2.7%) and infectious complications (2.6% vs. 3.7%) [58]. Phase 4 clinical trials are currently underway in adult, non-dialyzed CKD patients with IDA (ClinicalTrials.gov: NCT03236246). There were some alarming reports on increased level of amphiregulin in mice when treated with iron citrate. It suggests that there is a potential risk of intestinal carcinogenesis. Such an effect was not observed for iron sulfate [59].

Ferric pyrophosphate citrate (FPC) is an intravenous formulation marketed under the trade name Triferic (Rockwell Medical Inc.) approved for iron supplementation in adult dialyzed patients with CKD [60]. FPC is highly water-soluble, non-colloidal preparation containing trivalent iron (1 molecule of iron pyrophosphate and 2 molecules of iron citrate). The preparation was well tolerated and serious adverse events occurred at a similar frequency as in the placebo group, the most common being gastrointestinal side effects. A significant reduction in the requirement for therapy with erythropoiesis stimulating agents was also reported [60]. Further studies in dialyzed patients are ongoing (ClinicalTrials.gov: NCT04042324).

Iron maltol

Feracru in Europe or Accrufer in the United States (ferric maltol; Shield Therapeutics plc) is a new oral iron formula that consists of a stable trivalent iron complex bound with three maltol ligands. It is believed that the ratio of maltol to iron in this formula prevents the formation of iron hydroxide polymers and promotes iron absorption at a neutral pH of the gastrointestinal tract [61]. Iron trimaltol possesses both hydrophilic and lipophilic properties, and after oral administration, iron reaches the intestinal mucosa in a complexed form, which may allow for more effective uptake of elemental iron by enterocytes, especially when compared to iron salts. The complex does not pass through the intestinal mucosa. It is broken down into iron and maltol and both are absorbed separately [62]. Based on the summary of medicinal product characteristics, it is concluded that Feracru should not be used in patients with exacerbation of inflammatory bowel disease or inflammatory bowel disease with hemoglobin <9.5 g/dL. In addition, it was shown that excessive use of the preparation may cause toxic effects, especially in children. The manufacturer warned that Feracru must not be given to children. But, a randomized,

double-blind, placebo-controlled trial in more than 300 patients with ulcerative colitis or Crohn's disease and IDA demonstrated comparable safety of iron maltol to placebo with no exacerbations of IBD [63]. There was also a significant improvement in Hb levels, and 2/3 of patients shown normalization of Hb levels after 12 weeks of administration of 30 mg of iron maltol twice a day [63]. In another phase 3 study of iron maltol in IDA in the course of inflammatory bowel disease, the effectiveness and normalization of Hb parameters was demonstrated in 80% of patients during 20–64 weeks of therapy, with good tolerability and safety profile [64]. Iron maltol is of great interest to researchers. The recruitment for Phase 1 trial of iron maltol in children and adults with IDA (in various doses) has been completed just now (ClinicalTrials.gov: NCT03181451). Currently, several interventional clinical trials with iron maltol are in recruitment phase, i.e., for patients with IDA and heart failure (ClinicalTrials.gov: NCT03774615), IDA and pulmonary hypertension (ClinicalTrials.gov: NCT03371173), with CKD (ClinicalTrials.gov: NCT02968368), with IBD compared to an intravenous formulation (ClinicalTrials.gov: NCT02680756), and in hospital practice (ClinicalTrials.gov: NCT03247816).

Other drugs for IDA therapy

Research is underway on nanomaterials delivering iron to cells to improve the bioavailability and, at the same time, the tolerance of oral treatment [65–68]. The studies include biocompatible iron nanoparticles (Fe_3O_4) with the addition of vitamin C [68]. Studies of Fe and Fe/Zn nanocompounds produced by scalable flame aerosol technology are conducted in rats. So far, it has been shown that these nanocompounds are characterized by high bioavailability (comparable to iron sulfate) and do not cause stool discoloration [65]. One of the most promising nanomaterials used in animal models is iron hydroxide adipate tartrate (IHAT) [67]. The results of a controlled, double-blind, three-arm trial of IHAT in children with IDA aged 6–35 months in Gambia has shown that iron deficiency was eliminated and Hb was improved without inducing gastrointestinal side effects. In addition, a beneficial effect on the intestinal microflora was observed, including the reduction of pathogenic intestinal flora. IHAT has shown effectiveness similar to iron sulfate in terms of IDA treatment effects with a lower risk of diarrhea [69]. In the future, more research is expected on the effects of the microbiome on iron management and the treatment of anemia. Existing studies indicate the role of iron in the composition of the intestinal microflora, and this, in turn, may translate into the formation of intestinal inflammation or carcinogenesis.

Conclusions

The emergence of new oral iron preparations has widely expanded the possibilities of iron supplementation in IDA, especially in the presence of concomitant diseases such as CKD, HF, inflammatory bowel diseases, or cancer. Some studies indicate that sucrosomial iron and iron citrate complexes can replace intravenous iron under certain conditions. Sucrosomial iron is highly bioavailable and well tolerated due to its innovative structure and absorption via various

routes. Iron citrate complexes, in addition to good absorption in various pH conditions, lower phosphate concentration, which is beneficial for patients with CKD. Iron maltol is currently being studied in IDA patients with various comorbidities. New nanomaterials are being developed to deliver iron innovatively to cells. However, all these substances require further studies in larger patient populations to assess the actual effectiveness and safety of the therapy.

Authors' contributions

SSM – the only author.

Conflict of interest

None.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments; Uniform requirements for manuscripts submitted to biomedical journals.

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