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Review

Sucrosomial® Iron: A New Generation Iron for Improving Oral Supplementation

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Abstract: Iron deficiency (ID) is usually treated with oral iron salts, but up to 50% of patients complain of gastrointestinal side effects, leading to reduced treatment compliance. Intravenous (IV) iron formulations are increasingly safer, but there is still a risk of infusion and hypersensitivity reactions and the need for a venous access and infusion monitoring. Sucrosomial® iron (SI) is an innovative oral iron formulation in which ferric pyrophosphate is protected by a phospholipid bilayer plus a sucrester matrix (sucrosome), which is absorbed through para-cellular and trans-cellular routes (M cells). This confers SI unique structural, physicochemical and pharmacokinetic characteristics, together with high iron bioavailability and excellent gastrointestinal tolerance. The analysis of available evidence supports oral SI iron as a valid option for ID treatment, which is more efficacious and better tolerated than oral iron salts. SI has also demonstrated similar effectiveness, with lower risks, in patients usually receiving IV iron (e.g., chronic kidney disease, cancer, bariatric surgery). Thus, oral SI emerges as a most valuable first option for treating ID, even more for subjects with intolerance to or inefficacy of iron salts. Moreover, SI should be also considered as an alternative to IV iron for initial and/or maintenance treatment in different patient populations.

Keywords: anemia; iron deficiency; oral iron salts; intravenous iron; Sucrosomial® iron; M cells; bioavailability; tolerability; efficacy

1. Introduction

As of 2010, data from 187 countries reveals that anemia affected up to one third of the global population, though prevalence varied widely across regions, with iron deficiency (ID) being responsible for about 50% of anemia cases [1]. In a systematic analysis for the Global Burden of Disease Study 2016, iron-deficiency anemia (IDA) was the fourth leading cause of years lived with disability, especially in women [2]. Thus, prophylaxis and management of ID is a first order public issue. Main causes of ID are increased demands, reduced absorption and/or increased loss [3,4] (Table 1).

Table 1. Main causes of iron deficiency.

- ***Increased demands:***
  - Body growth (infancy and childhood)
  - Pregnancy and lactation
  - Recovery from blood loss
  - Treatment with erythropoiesis stimulating agents
- ***Limited external supply or absorption***
  - Poor intake
  - Inappropriate diet with deficit in bioavailable iron and/or ascorbic acid (including excess of dietary fiber, phenolic compounds from tea or coffee, and soya products)
  - Malabsorption (autoimmune atrophic gastritis, gastric resection, bariatric surgery, inflammatory bowel disease, celiac disease, non-celiac gluten sensitivity, *Helicobater pylori* infection)
  - Medications (AntiH_2, PPI, antacids, etc.)
  - Increased hepcidin levels (e.g., IRIDA or ACI)
  - Molecular defects in iron transport proteins (e.g., heme oxygenase or DMT1 deficiencies)
- ***Increased iron losses:***
  - Bleeding trauma
  - Gastrointestinal bleeding (peptic ulceration, neoplasia, inflammatory bowel disease, vascular malformations, medications [anti-inflammatory, anti-platelet or anticoagulant agents])
  - Genitourinary bleeding
  - Menses and multi-parity
  - Multiple diagnostic phlebotomies (medical "vampirism")
  - Blood donation
  - Dialysis (particularly hemodialysis)

ACI, anaemia of chronic inflammation; AntiH_2, histamine H_2 receptor antagonists; DMT1, divalent metal transporter 1; IRIDA, iron-refractory iron deficiency anemia; PPI, proton pump inhibitors.

Nevertheless, prevalence and consequences of ID may also vary depending on the clinical setting considered [5–13] (Figure 1). Following diagnosis of ID, it is especially relevant to find and address the underlying cause, especially in unexplained and/or recurrent cases, as well as to choose the therapeutic option that safely meets patient's needs [14–17].

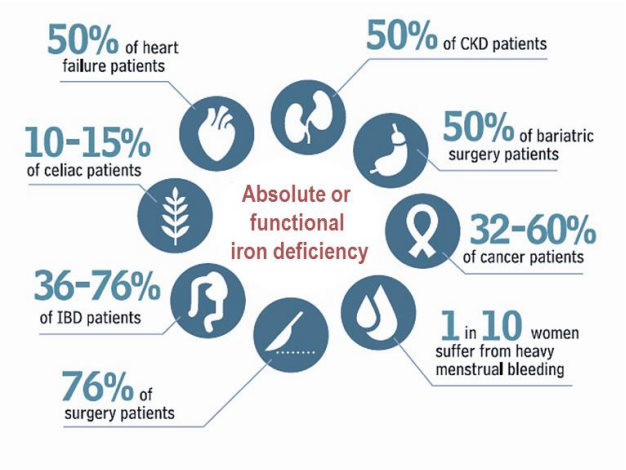

Figure 1. Prevalence of iron deficiency across pathologies (data taken from references [5–13]).

2. Diagnosis of Iron Deficiency

A correct diagnosis of ID is essential for a safe treatment, but it is sometime elusive. Importantly, the absence of anemia does not exclude ID, because a normal individual must store his iron before the hemoglobin (Hb) falls to values defined by World Health Organization (WHO) as anemia (Hb <

12 g/dL for women and Hb < 13 g/dL for men). In fact, the WHO declares that "mild anemia" is a misnomer, as ID could be well advanced and display clinical symptoms before Hb reaches the threshold for anemia [18]. The role of non-anemic ID as a disease looking for recognition has been recently reviewed: ID is the disease, anemia just one of its consequences [17,19].

Patient history (including signs and symptoms of ID and co-morbidities) and previous iron supplementation give some clues. In individuals without anemia, chronic fatigue is the most important symptom (iron is needed for the enzymes involved in energy production). However, generally, clinicians often do not relate chronic fatigue with ID. As a result, ID without anemia is almost invariably a casual laboratory finding [20].

In patients with Hb level within the normal range, ID should be suspected if a low mean corpuscular hemoglobin (MCH; normal range 28–35 pg) or an increased red cell distribution width (RDW, normal range 11–15) is present [4,21]. The most accurate definition of true ID is a serum ferritin concentration < 30 ng/mL (sensitivity 92%, specificity 98%), though lower values are used in many laboratories [22] (Figure 2). A serum ferritin < 100 ng/mL with a transferrin saturation (TSAT) < 20% is also indicative of ID, especially in the presence of inflammation (Figure 2). In contrast, serum ferritin > 100 ng/mL with a TSAT < 20% usually indicates iron sequestration (also referred to as functional iron deficiency, FID). Treatment with erythropoiesis-stimulating agents (ESA) may also result in FID, as mobilization from stores may be not rapid enough to meet the increased bone marrow demands on iron (Figure 2) [4,21,23]. This provides the basis for iron supplementation in most patients on ESA treatment.

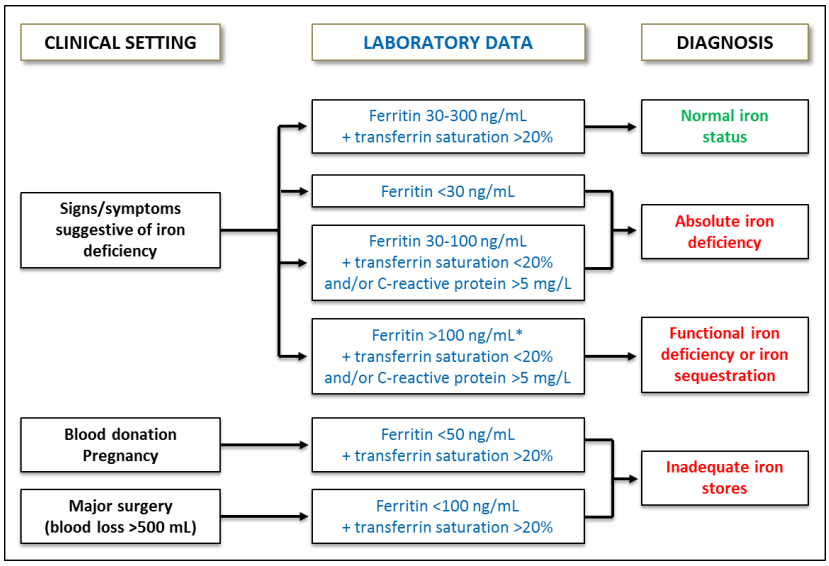

Figure 2. Laboratory assessment of iron status. * Low reticulocyte Hb content (<28 pg), increased hypochromic red cells (>5%) or high soluble transferrin receptor to log ferritin ratio (>2) could identify a component of absolute iron deficiency in the presence of inflammation-induced high ferritin level.

However, as it is an acute phase reactant, high ferritin levels do not excluded ID in patients presenting with an inflammatory status. In these cases, other parameters, such as a low reticulocyte Hb content (<28 pg), increased hypochromic red cells (>5%) or high soluble transferrin receptor to log ferritin ratio (>2), indicate a component of true ID. Should it be present, iron supplementation may provide a benefit [4,14,21].

3. Treatment Options for Iron Deficiency

In addition to searching for and addressing the underlying cause, if possible, ID could be treated with oral iron, intravenous (IV) iron and/or blood transfusion, depending on patient's Hb levels, tolerance and co-morbidity. Whether it is a new onset or recurrent, explained or unexplained ID should also be considered for treatment choice.

3.1. Oral Iron Supplementation

Oral iron supplements, given as ferrous or ferric salts, are usually the first line of treatment for uncomplicated ID, because their availability, ease of administration, and relatively low cost [14,15]. Oral iron has been usually prescribed at high dose (100–200 mg elemental iron) to be taken 1–3 times a day. However, bioavailability is 10% to 15% for ferrous iron preparations (sulfate, gluconate, fumarate, etc.) and even lower for ferric iron salts or ferric iron complexes (amino acids, polysaccharide, ovo-albumin, etc.). Co-administration of others drugs, such as proton pump inhibitors or antacids, or meals, and the presence of an inflammatory status may further hamper the absorption of oral iron salts [24]. This may prolong the duration of treatment or even render it ineffective [24]. In addition, up to 50% of patients on oral iron (depending on the iron formulation) report gastrointestinal side effects, due to direct toxicity of ionic iron, which may lead to reduced tolerance and adherence to iron supplementation [25,26].

Single low doses of iron supplements (40–60 mg/day) are associated with less gastrointestinal side effects and lower hepcidin secretion, resulting in better treatment compliance and enhanced fractional absorption [27,28]. In a randomized study, 90 octogenarian patients with IDA received 15 mg, 50 mg or 150 mg of elemental iron per day. At two months, there were no between-group differences in the levels of Hb (mean increase 1.4 g/dL in all groups) or ferritin, but adverse effects were significantly more common with higher doses [29]. Therefore, low single daily dose (40–60 mg) and/or single alternate day dose (80–100 mg) are preferred [27–29]. Though not formally proven, this emerges as a new paradigm for oral iron supplementation in ID treatment [21].

3.2. Intravenous Iron Supplementation

Should the patient develop intolerance to one iron salt or oral iron salt not be efficacious, switching to another oral iron formulation or to intravenous (IV) iron may be appropriate [15]. Different IV iron formulations have been made commercially available for clinical use, such as ferric gluconate (FG), iron sucrose (IS), low molecular weight iron dextran (LMWID), ferric carboxymaltose (FCM), ferumoxytol (FXT), or iron isomaltoside 1000 (ISM). All of them have been shown to have a dose-dependent efficacy for correcting ID [17,24]. However, "newer" IV iron formulations, such as FCM or ISM, which allow short-time (15–60 min) infusion of high iron doses (1000 mg or more) are preferred by both physicians and patients compared to "older" IV formulations [17,24]. Nevertheless, though increasingly safer, IV iron formulations are more expensive than oral iron and still bear the need for venous access (side effects at the injection site may occur) and infusion monitoring (there is still a risk of infusion and hypersensitivity reactions) [30]. In this regard, the European Medicines Agency states that "IV iron products should be administered only when staff trained to evaluate and manage anaphylactic reactions, as well as resuscitation facilities, are immediately available" [30]. In addition, except for the chronic kidney disease population [7], data on long term safety of IV iron are scant [24].

3.3. Red blood Cell Transfusion

A patient presenting with severe IDA and alarming symptoms (e.g., hemodynamic instability) and/or risk criteria (e.g., coronary heart disease) should be treated with red blood cell transfusion using the minimal amount necessary to achieve clinical stability. Adhering to patient-adapted restrictive transfusion criteria and transfusing one unit at the time, with post-transfusion reassessment, is strongly recommended by most guidelines [6,31–34].

Red blood cell transfusion produces a rapid, albeit transient, rise in Hb, thus increasing oxygen-carrying capacity. However, severe IDA will recur unless the underlying cause is identified and addressed. After hemodynamic stability has been achieved with red blood cell transfusion, additional iron supplementation should be considered [17].

4. Sucrosomial® Iron: Preclinical Data

4.1. Composition and Structure

Commonly used oral iron salts are poorly absorbed, with unabsorbed iron leading to gastrointestinal side effects [25]. Newer oral iron supplements have been formulated to have increased tolerability [26]. However, there was still a need for new carriers that not only protect the iron but also enhance its intestinal absorption, thus reducing dosage and side effects [35].

Sucrester is a surfactant derived from the esterification of fatty acids with sucrose (sucrose esters), which has recently been shown to behave as absorption enhancer, because of its ability to reduce intestinal barrier resistance, thus facilitating the passage through para-cellular and trans-cellular routes [36,37]. Sucrester effects depend on both the hydrophilic-lipophilic balance and the fatty acid chain length; therefore, the choice of the appropriate raw material is crucial for developing a formulation with absorption enhancer properties. While there is evidence of the enhancer properties of sucrose esters for accumulation of drugs in CACO-2 cells [38] and for intestinal permeability in animals [39], its use for oral medicinal product administration has been scarcely studied.

Sucrosomial® iron (SI), developed by Alesco srl (Pisa, Italy), represents an innovative oral iron-containing carrier in which ferric pyrophosphate is protected by a phospholipid bilayer membrane, mainly from sunflower lecithin, plus a sucrester matrix. Further stability and coating are obtained adding other ingredients (tricalcium phosphate, starch), forming the "sucrosome" and allowing SI to be gastro-resistant and carried through the intestinal tract, without side effects derived from the interaction between iron and intestinal mucosa (Figure 3). To date, in vitro studies have shown that SI is mostly absorbed as vesicle-like structure, bypassing the conventional iron absorption pathway. Due to its behavior at the gastrointestinal tract, SI is well tolerated and highly bioavailable compared to conventional iron salts [40].

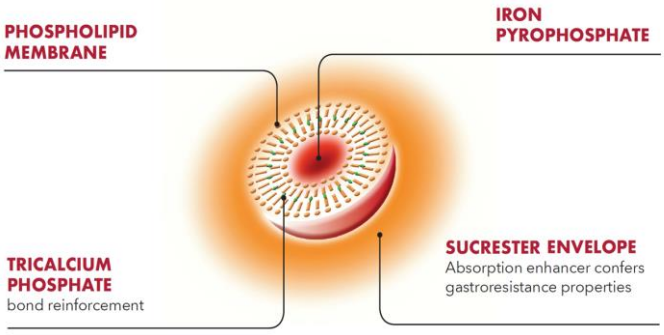

Figure 3. Schematic structure of Sucrosomial® iron.

4.2. Gastro-Resistance and Intestinal Absorption

The presence of sucrester confers gastro-resistance properties to SI [41], as demonstrated in *in vitro* studies performed using a simulated gastric fluid digestion (pH 1.2). Over 30 to 120 min digestion time, the release of ferric iron (III^+) from SI was very low (<5%) compared to that from a sucrester-free iron preparation (75–85%) (Figure 4A) [41].

Gastro-resistance allows the intact sucrosomes to reach the intestinal mucosa, where they are absorbed. Polled data from several studies indicate the presence of different pathways involved in SI absorption. *Ex-vivo* permeation experiments, carried out using the excised rat intestine model, have shown that the presence of sucrester protects trivalent pyrophosphate iron in SI against enzymatic reduction and promotes its absorption across the intestinal epithelium, by a DMT-1 independent pathway, as it was not affected by BPDS activity (bathophenanthroline disulfonic acid, a divalent iron chelator) [40].

The presence of the phospholipids and sucrester matrix allows pyrophosphate iron in SI to be absorbed as vesicle-like structure through para-cellular and trans-cellular routes. In vitro experiments using the MatTek EpiIntestinal™ human 3D tissue model have confirmed the presence of vesicle-like structures during the intestinal absorption of SI and its different absorption kinetics compared to ferrous sulfate (FS) and ferrous bisglycinate (FeBIS) [42]. Over time, a greater increase

of iron concentration at basolateral compartment was observed in tissues treated with SI (2.7 ± 1.7 µg/mg protein) compared to samples treated with FS (1.3 ± 1.1 µg/mg protein) and FeBIS (1.6 ± 1.1 µg/mg protein), indicating an endocytosis-mediated cellular uptake confirmed with transmission electron microscopy analysis [42].

Microfold cells of the Peyer's patches (M cells) are involved in the transfer of particles and microbes from the luminal side of the intestine to the *lamina propria*, where they are presented to immune cells. M cells have been shown to provide a pathway for delivering orally administered vesicle-like particles to the lymphatic system [43,44]. However, the transfer efficacy of this pathway has also been shown to be greatly influenced by the physicochemical properties of the transported particles [43,44]. The possible role of an M cell-mediated pathway in SI absorption was investigated using an in vitro CACO2/RajiB co-culture system. Experimental data show that the presence of M cells (RajiB cells) increased the absorption of SI, but not that of conventional oral iron salts as FS or FeBIS (Figure 4B). This evidence confirms that M cells can support the intestinal absorption of SI. In *ex-vivo* experiments using isolate rat intestine and fluorescein labeled SI, it has been demonstrated that, after passing through M cells, SI was taken up by CD68+ macrophages [42].

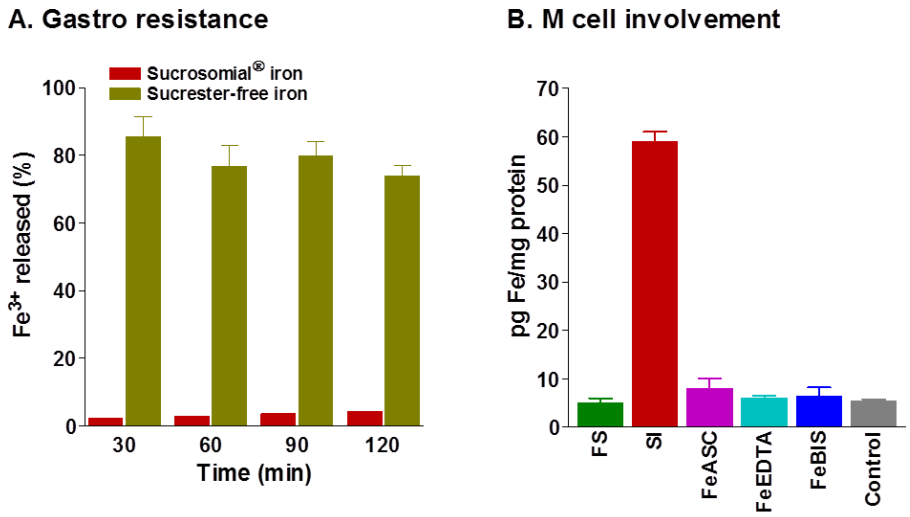

Figure 4. Gastro-resistance and intestinal absorption of Sucrosomial® iron. (**A**) Gastro-resistant properties of Sucrosomial® iron compared to a sucrester-free iron preparation in an in-vitro simulated gastric fluid digestion at pH 1.2. (**B**) M cells involvement in Sucrosomial® iron uptake was evaluated using in vitro CACO2/RajiB co-culture. Iron to protein ratio was significantly increased in co-culture cells treated with Sucrosomial® iron (SI) compared to other oral iron formulations: ferrous sulfate (FS), ferrous ascorbate (FeASC), ferrous ethylene-diamine-tetra-acetate (FeEDTA), ferrous bisglycinate (FeBIS), and control (no iron) (data are mean ± SEM, * $p < 0.05$) (Adapted from references [41,42]).

4.3. Bioavailability

Most probably, the involvement of different cellular routes in SI absorption underlies its high bioavailability, and may explain its efficacy for improving hemoglobin and ferritin concentrations. Data from CACO-2 cell cultures show that administration of SI increases 3-fold ferritin accumulation compared to ferrous sulfate and 3.5-fold compared to phospholipid containing ferric pyrophosphate (Lipofer®) or micronized, dispersible ferric pyrophosphate (SunActive®) (Figure 5A), indicating that SI technology increases ferritin iron accumulation within enterocytes [45]. Furthermore, in vitro experiments comparing SI with commercially available iron salts show that SI was able to significantly increase ferritin concentration in CACO-2 cells compared to tested iron salts (Figure 5B) [41].

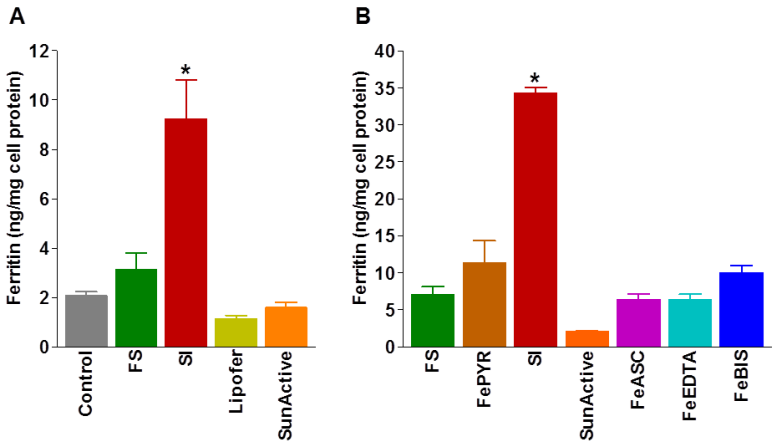

Figure 5. Bioavailability experiments on CACO-2 cells. Ferritin expression by cells treated with Sucrosomial® iron (SI) was significantly increased compared to cells treated with ferrous sulfate (FS), phospholipid containing ferric pyrophosphate (Lipofer®), or micronized, dispersible ferric pyrophosphate (SunActive®) (**A**) or different iron salts, FS, ferric pyrophosphate (FePYR), ferrous ascorbate (FeASC), ferrous ethylene-diamine-tetra-acetate (FeEDTA), ferrous bisglycinate (FeBIS), and control (no iron) (**B**) (Data are mean ± SEM, * $p < 0.001$ SI vs. other iron compounds) (Adapted from references [41,45]).

Data from cell cultures show that SI was able to increase ferritin expression in enterocytes in vitro, but this evidence was not sufficient to demonstrate high bioavailability of SI in vivo. Therefore, SI bioavailability was subsequently investigated in iron deficient new-born piglets and mice. In piglets, a 4-week course of oral SI supplementation efficiently prevented deterioration of the hematological status and contributed to the recovery from IDA as shown by significantly increase in Hb concentration compared to iron dextran treated animals. In addition, oral SI supplementation increased duodenal L-ferritin protein levels compared with animals treated with parenteral iron dextran (Figure 6A) [46].

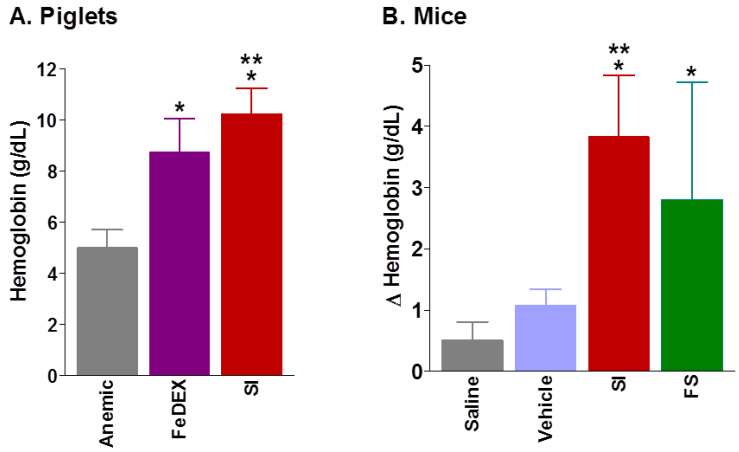

Figure 6. Iron supplementation in anemic piglets and mice. (**A**) Hemoglobin concentration in anemic piglets treated with iron dextran (FeDEX) or Sucrosomial® iron (SI) (Data are mean ± SD; * $p < 0.001$, treatment vs. anemic; ** $p < 0.001$, SI vs. FeDEX). (**B**) Change in hemoglobin levels in anemic mice after 14-day treatment with Sucrosomial® iron (SI) or ferrous sulfate (FS). (Data are mean ± SD; * $p < 0.01$, SI or FS vs. saline; ** $p < 0.05$, FS vs. vehicle) (Adapted from references [46,47]).

As for anemic mice treated with iron administered via gavage for 2 or 4 weeks, SI was able to improve hemoglobin levels and iron status (Figure 6B) [47]. Bioavailability data obtained from animals are interesting, as they indicate that different animals affected by IDA respond to oral SI

supplementation in a similar manner, and that the efficacy of SI is comparable with all forms of oral iron salts. Remarkably, the efficacy of SI has been demonstrated not only in animal models of uncomplicated IDA, but also in some clinical conditions in which the absorption of oral iron is drastically reduced (e.g., celiac disease, post-bariatric surgery, ACI, IRIDA) [48–52].

4.4. Distribution

Usually iron distribution and storage is measured by the quantification of total iron and ferritin expression in target tissues. Ferritin-bound iron indicates the ability of the cell to internalize and store iron and, indirectly, the absorption of the administered iron. Anemic piglets and mice treated with SI were able to store iron in ferritin in spleen and liver. Moreover, a mild but significant increase of serum iron and transferrin saturation was observed in both IDA animal models [46,47].

A bioavailability study was also performed in healthy rats treated with ferric pyrophosphate or SI, in which concentrations of trivalent iron in blood were measured over time (5 h). Blood concentrations of trivalent iron were higher in animals treated with SI after the first 3 h. Pharmacokinetic profiles show that area under the curve (AUC) and maximal plasma concentration of iron (C_{max}) for SI were significantly higher than those for ferric pyrophosphate. Furthermore, 5 h after the oral administration, SI but not ferric pyrophosphate led to a measurable increase of trivalent iron content in liver and bone marrow [53]. These data suggest a greater bioavailability for SI, and that iron supply exceeding the requirements for hematopoiesis and metabolic processes is stored in the hepatocytes [54].

4.5. Iron Homeostasis

Hepcidin, a 25-amino acid peptide synthetized by hepatocytes, regulates systemic iron homeostasis and it levels can be increased in response to inflammation or iron overload [55]. Similarly, oral supplementation with iron salts also induces hepcidin up-regulation to regulate iron release into the bloodstream and then to target organs [35].

The effects of oral supplementation with ferrous sulfate or SI, given at the same concentration (1 mg/kg/day), on liver hepcidin mRNA and circulating hepcidin levels were investigated in IDA mice. While SI-treated mice showed a minor, non-significant increase in liver hepcidin mRNA and serum hepcidin levels, both were significantly increased in ferrous sulfate-treated animals. In parallel, FS induced the expression of two inflammatory markers, suppressor of cytokine signaling 3 (Socs3) and C-reactive protein (CRP), while SI did not [47]. This suggests that FS supplementation induces hepcidin up-regulation through a double mechanism. Firstly, a direct effect of the absorbed iron on peri-portal hepatocytes, as observed in ID women receiving FS at doses ≥60 mg/day [27]. Secondly, direct toxicity of non-absorbed iron on intestinal mucosa that induces an inflammatory response [56]. In contradistinction, most SI is not released to the portal blood stream, but to the lymphatic circulation (M cells route) and later to the arterial circulation, before reaching the liver. Moreover, ferric pyrophosphate in SI does not interact with duodenal mucosa, as it is protected by the sucrosome, and it has been also suggested that phospholipidic bilayer carriers may also exert anti-inflammatory properties [57]. Such a different behavior of SI could be relevant since hepcidin reduces iron availability by inhibiting cellular iron export.

5. Sucrosomial® Iron for Management of Iron Deficiency in Different Clinical Settings

As stated above, SI has unique structural, physicochemical and pharmacokinetic characteristics, together with high iron bioavailability and excellent gastrointestinal tolerance. These properties enable SI to be the most suitable formulation for oral treatment of ID, even in clinical settings (e.g., chronic kidney disease [CKD], cancer, bariatric surgery, etc.) where IV iron seemed to be the only therapeutic option [48–52]. We will review the efficacy and safety of oral SI for treating ID in most common clinical scenarios.

5.1. Obstetrics

Iron deficiency during pregnancy continues to present a significant health problem throughout the world. There is evidence that ID and IDA are associated with an increased risk of poor pregnancy outcome (e.g., low birth weight, prematurity), low neonatal iron deposits, preeclampsia and post-partum hemorrhage [5]. In a propensity score analysis (n = 12,470), severe pregnancy anemia was also associated with an increased risk of peri-partum mortality [58]. In the postpartum period, anemia is associated with decreased physical performance, reduced cognitive abilities and impaired lactation [5].

In order to reduce the risk of low birth weight, maternal anemia and iron deficiency, a recent consensus statement recommends daily oral supplementation with 30–60 mg iron and 400 μg folic acid, as part of routine antenatal care [5]. However, compliance with recommended oral iron among pregnant women is variable, mostly due to gastrointestinal side effects. Multivitamin and mineral compounds are not the best way for supplementation, mainly when ID or IDA is present, as most of them do not contain adequate amounts of iron or vitamins B_{12}, C or D. Indeed, an epidemiological study in Portugal found a very high prevalence of IDA among pregnant women (54.2%), despite the fact that over 80% of them were on iron supplementation, mostly given through multivitamin and mineral products [59].

In this regard, a recent study non-anemic pregnant women, presenting with Hb > 10.5 g/dL at 12–14 weeks of gestation, were randomly assigned to receive no iron (control; n = 20), ferrous iron 30 mg/day (FI; n = 20), SI 14 mg/day (SI-14; n = 20) or SI28 mg/day (SI-28; n = 20) up to 6 weeks postpartum (Table 2). Compared to control and FI group, the SI-28 group showed significantly higher Hb levels at 28 weeks and in postpartum period. Ferritin levels at 20 and 28 weeks and at 6 weeks postpartum ($p < 0.01$) were significantly higher in SI-28 group compared to control. Interestingly, fewer women from the SI-28 group developed anemia (10%), compared to control (30%), FI (25%), and SI-14 (25%). Moreover, no differences in hematological parameters were observed between SI 14 mg/day and FI 30 mg/day, thus demonstrating higher bioavailability and allowing reducing doses and side effects [60] (Table 2).

In a series of 148 consecutive deliveries, 8 non-anemic women (mean Hb: 12.1 g/dL), who developed postpartum anemia due to bleeding (mean: 858 mL; range: 700–1600 mL), received SI (60 mg twice daily). After one week, mean Hb increase was 1.5 g/dL, and no gastrointestinal or systemic side effects were witnessed [61].

Thus, published evidence on SI in preventing anemia during pregnancy are very promising, and large studies to further evaluate the role of SI in pregnancy and in the postpartum period would be helpful (Eudra CT: 2017-000994-35).

5.2. Oncology

Both ID and IDA are highly prevalent onco-hematological patients. IDA and chemotherapy-induced anemia (CIA) are generally managed with red blood cell transfusion, ESAs and/or iron supplementation. However, there is controversy on safety and cost issues regarding different iron compounds and administration routes [23,62].

A recent position statement recommends investigating the presence of anemia and/or iron deficiency in all cancer patients, but especially in those scheduled for cytotoxic chemotherapy, radiotherapy or surgery. This should be done before and during treatment to plan the most appropriate therapeutic strategy [23].

According to most recent European Society of Medical Oncology guidelines, patients with CIA (Hb ≤ 11 g/dL or Hb decrease ≥ 2 g/dL from a baseline level ≤ 12 g/dL) and absolute ID (serum ferritin < 100 ng/mL) should receive iron treatment to correct ID. In the case of FID (TSAT < 20% and serum ferritin > 100 ng/mL), iron treatment should be given before the initiation of and/or during ESA therapy (with both originator and biosimilar products approved by the European Medicines Agency), or as mono-therapy [6].

Regarding the iron formulation to use, these guidelines indicate oral iron to be considered only for patients with both absolute ID and non-inflammatory conditions (CRP < 5 mg/L) [6]. Even if guidelines recommend the use of IV iron in cases of FID, they stated that long-term safety of IV iron in oncology has

not yet fully established [6]. Therefore, SI could be taken in consideration in cases of inflammatory conditions and anemia, as SI absorption does not seem to be affected by hepcidin [23,35].

In several small case-series and pilot studies of anemic oncologic patients, with or without chemotherapy, oral SI (30–60 mg/day for 2–6 months) was shown to increased Hb levels with very few gastrointestinal side effects (Supplementary Material, Table S1). More recently, a retrospective study of patients presenting with moderate CIA (Hb 8–10 g/dL) and no ID or FID assessed the performance of oral SI (30 mg/day; n = 33) in improving Hb response to ESA (darbepoetin 500 μg/3 weeks), compared to IV FG (125 mg/week; n = 31) [51] (Table 2). After 8 weeks of treatment, there were no differences between groups in Hb response (70% vs. 71%, respectively), as defined by an increment in Hb ≥ 2 g/dL and/or a final Hb ≥ 12 g/dL. There were also no differences in red cell transfusion rates (one patient in each group) or change in quality of life. Oral SI was well tolerated with only one patient showing gastrointestinal toxicity, whereas two infusion reactions were needed with IV FG.

5.3. Nephrology

Iron deficiency is one of the main causes of anemia in patients with CKD, and iron supplements along with ESAs constitute the basis of its therapy, both in that not on dialysis (ND-CKD) and in hemodialysis-dependent (HD-CKD), but disparities exist in guidelines and position papers for anemia treatment across the world [7,63].

Though mortality and adverse effects rates in CKD patients receiving oral or IV iron supplementation are similar, a meta-analysis (24 studies, 3187 patients) found that hypotensive reactions were more frequent with IV iron, whereas more gastrointestinal adverse events were observed with oral iron [64]. A recent randomized, controlled trial in 128 anemic CDK patients suggested a possible higher incidence of cardiovascular events and hospitalization for infection in the IV iron arm compared to the oral iron arm [65]. In contrast, a trial evaluating IV versus oral FS in 626 anemic ND-CKD patients with ID and not receiving ESA therapy, found no difference in infection rates or cardiac events between patients receiving higher FCM dose (500–1000 mg/4 weeks), lower FCM dose (200 mg/4 weeks) or oral FS (200 mg/day) during the 56 weeks follow-up (3.9%, 3.3%, and 3.8%, respectively) [66]. Of note, in this trial only 21.6% of patients on oral iron showed an Hb increase of at least 1 g/dL, and <30% of early non-responders responded at any subsequent time point during follow-up, suggesting a benefit for earlier consideration of alternative therapy in this population [67]. In a cohort of 58,058 HD-CKD patients, IV iron doses greater than 400 mg/month were associated with higher cardiovascular death rates [68]. The conclusion should be that "too much iron is bad" for CKD patients, but further large clinical studies are needed (such as the on-going PIVOTAL trial; EudraCT Number: 2013-002267-25), whereas oral versus IV administration of iron is an on-going debate [24,63].

In several case series of ND-CKD patients (mostly with mild anemia), oral SI (30 mg/day), with or without ESA, was shown efficacious in maintaining and/or increasing Hb, ferritin and TSAT levels during different follow-up periods (from 3 to 24 months), with virtually no gastrointestinal side effects (Supplementary material, Table S2). In a randomized open-label trial, 99 ND-CKD patients with IDA (Hb ≤ 12 g/dL, ferritin ≤ 100 ng/mL, TSAT ≤ 25%) were assigned (2:1) to receive oral SI (30 mg/day) for 3 months or a total dose of 1000 mg of IV FG (125 mg/week) and followed-up for 4 month [50]. At the end of treatment period, Hb levels were similar in both groups (11.4 g/dL vs. 11.7 g/dL, respectively) though replenishment of iron stores was greater in the IV FG group (ferritin 86 ng/mL vs. 239 ng/mL, respectively; $p < 0.05$) (Table 2).

Though Hb concentrations decreased more rapidly after iron withdrawal, significantly fewer adverse events were observed in the oral ($p < 0.001$), whereas adherence to treatment was similar in the two groups. Therefore, this study shows that short-term, low-dose oral SI is as efficacious as IV FG for correcting anemia in ND-CKD patients, and suggests no risk for iron overload during its long-term use. Similar results were observed in two preliminary studies comparing oral IV and IV FG, with or without ESA, in 34 anemic HD-CKD patients (Supplementary Material, Table S2).

Recently, in three CKD patient populations (pre-dialysis, peritoneal dialysis, and post-transplant) who did not respond to conventional oral iron supplementation, Darbá et al. [69] assessed the economic impact of switching from intravenous iron (FCM or IS) to SI. Using a 4-year budget impact model (2017–2020), the progressive increasing of SI use (up to 10% of the market shares) would lead to over €750,000 savings.

5.4. Gastroenterology

Anemia is the most frequent systemic complication in *inflammatory bowel disease* (IBD), *celiac disease* (CD), *non-celiac gluten sensitivity* (NCGS) and *autoimmune atrophic gastritis* (AAG) [70]. In IBD patients, anemia is more frequent among those with Crohn's disease, though its prevalence in studies varies according to definition criteria, type of patients, and year of publication, but ID and ACD are the most common causes [9].

Oral iron supplementation in IBD patients may result in worsened disease symptoms (flares) which can be attributed not only to iron-induced oxidative stress, but also to microbiota alterations. After 3-month of iron supplementation, shifts in gut bacterial diversity and composition were found in IBD patients, with oral FS (120 mg elemental iron per day) differentially affecting bacterial phylotypes and fecal metabolites compared with IV iron sucrose therapy (3–4 doses of 300 mg) [71]. However, in an experimental model of colitis in mice (induced by administration dextran sodium sulfate [DSS]), the effect of dietary iron supplementation (500 mg/kg) on survival depended on the formulation used, and was either beneficial (FeBIS) or highly detrimental (ferric ethylene-diamine-tetra-acetic acid), most likely through modulation of the microbiota [72]. In addition, a hem-enriched intestinal lumen (due to hem-rich diet, hem-based iron supplementation or intestinal bleeding) led to changes in bacterial flora composition (with a decrease *Proteobacteria* and a reduction of *Firmicutes*) which were similar, though less pronounce, to those observed after DSS administration [72]. Therefore, oral iron supplementation in IBD patients with ID is challenging, and guidelines are prone to recommend the use of IV iron [9]. However, initial clinical data in IBD patients suggest that oral iron formulations with improved tolerability, such as SI or ferric maltol, may represent a viable alternative to IV iron [73].

In several case series of IBD patients with mild-to-moderate IDA (n = 92, including 46 intolerant to ferrous sulfate [74]), SI (30–60 mg/day for 2–3 months) has been shown efficacious in rising Hb concentrations (+0.92 g/dL), as well as ferritin and TSAT levels, with very few gastrointestinal side effects (Table 2) (Supplementary Material, Table S3). In comparative 2–3 month treatment courses, the efficacy of SI (30–60 mg/day; n = 38) in increasing Hb was higher than that of FS (105–210 mg/day, n = 14) (mean Hb change +2.7 g/dL vs. 1.4 g/dL, respectively), despite lower elemental doses (Supplementary Material, Table S3), and similar to that of IV iron sucrose (100 mg/session, up to 500–1000 mg) (mean Hb change: +1.7 g/dL vs. +1.8 g/dL, respectively) [75] (Table 2).

Celiac disease is a common intestinal autoimmune pathology, which presents with laboratory abnormalities, irritable bowel syndrome, osteopenia, fertility problems and iron deficiency [76]. A prospective study evaluated the efficacy of a 3-month course of SI supplementation (30 mg/day) in anemic patients with CD not tolerating oral FS (n = 24) (NCT02916654) [48]. Additionally, naïve patients were assigned to receive oral FS (105 mg/day) (n = 19). After a 3-month follow-up, a significant improvement in all iron parameters was observed in both groups. Both treatments increased Hb levels compared to baseline, with a similar proportion of patients presenting Hb values within the normal range (70% vs. 82%, respectively; p = ns), despite elemental iron dose with SI was one third of that with FS (Table 2). As evaluated by visual analog scale (VAS) scores, patients on SI

reported a lower severity of abdominal symptoms, and a higher increase in general well-being compared to those on FS [48].

Sucrosomial® iron (30 mg/day for 15 days, plus 15 mg/day for 75 days) has also been shown to be effective in treating IDA in a series of NCGS patients (n = 28) increasing Hb (+2.8 g/dL) and ferritin levels (+11 ng/mL) (Supplementary Material, Table S3).

Autoimmune atrophic gastritis is another autoimmune entity, may be triggered by *Helicobacter pylori* infection, in which autoantibodies against gastric parietal cells and/or intrinsic factor are characteristically present. Mucosal atrophy leads to hypo- or achlorhydria, and most AAG patients develop anemia, either due to cobalamin deficiency (older patients) or ID (younger patients) [70]. Importantly, AAG is responsible for 20–27% of IDA cases which are refractory to oral iron supplements, and use to be treated with IV iron [77].

To assess the efficacy of oral SI, 20 consecutive AAG women (100% with gastric parietal cells autoantibodies, 20% with intrinsic factor autoantibodies) with recently diagnosed IDA (Hb < 120 g/dL) were enrolled in a prospective observational study [78]. Patients received SI (120 mg/daily, either fasting or during meals) for 8 weeks. Only three patients were dropped out due to intolerance (2) or lack of compliance (1). Compared to baseline values, after 8 weeks there were significant increments in Hb (from 10.5 g/dL to 12.5 g/dL), ferritin (from 7 ng/mL to 27 ng/mL) and TSAT (from 8% to 18%) (Table 2).

Bariatric surgery, especially malabsorptive procedure, can be associated with a risk of nutritional deficiency, including iron, which increases over the years, being women of childbearing age are the most vulnerable group [10]. In a 4-year follow-up after gastric bypass or sleeve gastrectomy procedures at a single institution (n = 353, 73% women), the investigators found that ID prevalence was significantly reduced in men (17.2% vs. 40%), but significantly increased in women (31.5% vs. 26.1%), especially in those of child-bearing age (<50 years) [79]. In these settings, traditional oral iron formulations present clear and significant limitations regarding tolerance and efficacy, and patients use to be switched to IV iron.

A case-control study included 40 women of childbearing age who were receiving IV iron sucrose supplementation after bariatric surgery (300 mg every 3 months). Of those, 20 were switched to oral SI (28 mg/day for 3 months), while another 20 received a dose of IV iron sucrose (300 mg). Hemoglobin, ferritin, and TSAT levels were measured before and three months after treatment switch, and no between-group differences were found [49] (Table 2). Thus, for patients developing ID after bariatric surgery and requiring IV iron, oral SI could be an alternative maintenance therapy.

5.5. Cardiology

As stated above, iron is needed for proteins and enzymes involved in oxygen transport (hemoglobin), storage (myoglobin), and utilization for energy production (respiratory chain) in skeletal and cardiac muscle cells. ID with or without anemia affects 50% congestive heart failure (CHF) patients, and is independently associated with reduced physical performance, decreased quality of life and increased risk of mortality [8]. Treatment of ID, as defined by serum ferritin < 100 ng/mL or ferritin between 100–299 ng/mL and TSAT < 20%, in patient with chronic heart failure, is a strong recommendation from the European Society of Cardiology [80].

The mechanisms of ID in heart failure are still not well understood. Chronic heart failure is considered as a low-grade inflammatory status, which increases circulating levels of hepcidin. In turn, hepcidin binds ferroportin, especially at the enterocytes, promoting its internalization and degradation, thus preventing iron absorption, while iron recirculation from macrophages seems to be less affected [4,14,55]. The alteration in the composition of the intestinal microbiota, known as intestinal dysbiosis, may also contribute to perpetuate the inflammatory status [35]. High prevalence of malnutrition and reduced iron absorption due to intestinal edema could also be involved [35]. In a recent randomized controlled trial in CHF patients, oral iron polysaccharide (150 mg, bid) was demonstrated inefficacious for correcting ID [81]. In contrast, European Society of Cardiology guidelines recommend the administration of IV iron for treating ID in this patient population [80].

However, a prospective pilot study has evaluated the possible role of oral SI supplementation in 30 patients with CHF and ID iron deficiency, with or without anemia [82]. Twenty patients received oral SI (30 mg/day for 3 months) and 10 served as controls (no iron). All were on stable, evidence-based medical therapy for at least 1 month, and there were no differences in baseline clinical and laboratory parameters between groups. At 3 months, SI treatment improved iron parameters, while Hb levels remained stable. There were also an improvement in quality of life, as assessed by Kansas City Cardiomyopathy Questionnaire (from 55.7 to 61.8; $p = 0.038$), and a trend towards a longer 6-min walked distance (from 318 m to 332 m; $p = 0.065$) and lower B-natriuretic peptide (from 643 to 535; $p = 0.360$). All patients in SI group were adherent to protocol and no side effects were witnessed. No change in any of the assessed parameters was observed in the control group. These results are in line with those from three small case-series (n = 29) (Supplementary Material, Table S4), but large, confirmatory studies are needed. In this regard, 2 randomized controlled trials comparing oral SI with oral ferrous bisglycinate or placebo (PREFER-HF study) or oral SI with IV FCM (IVOFER-HF study) are currently on-going.

5.6. Internal Medicine

Anemia is a frequent condition among hospitalized surgical and critically ill patients, compromising their clinical outcome. However, the role of anemia as a risk factor for poor outcome in other hospitalized patients has been hardly investigated. In a random sample of patients admitted to the internal medicine ward in 2015, prevalence (53%) and severity (46% moderate, 7% severe) of anemia was high, and consistent with ACI, blood loss, and/or hemodilution [83]. It seemed to be linked to older age, higher Charlson comorbidity index, longer hospital essay and increased in-hospital mortality, but it was underdiagnosed and undertreated [83]. On admission to the internal medicine ward, data from 771 consecutive patients revealed that 67% presented with anemia, which was associated with an increased risk of in-hospital mortality (RR 1.82, 95% CI 1.21–2.74) [84]. Iron deficiency (58%), with (41%) or without (18%) anemia, was also highly prevalent [84]. Therefore, an appropriate anemia management protocol for this patient population should be established, including appropriate provision of iron supplementation.

Patients with *myelodysplasia* (MSD) frequently exhibit anemia with FID, for which IV iron may be effective [6]. However, preliminary data suggested that oral SI may be as effective as IV iron in MSD patients (Supplementary Material, Table S5). More recently, the efficacy of SI (28 mg/day) to support the erythropoietic response to originator (group A) or biosimilar (group B) epoetin-α was studied in 92 MSD patients with and refractory anemia. Patients also received vitamin B_{12} (400 mg/day orally) and calcium levofolinate (7.5 mg/day orally) to avoid deficiencies of maturation factors [85]. Responder rates (as defined by an Hb increment ≥ 1.5 g/dL after 3 months of epoetin treatment) were similar in both groups (50% and 43%, respectively), and higher that that reported in the literature [86], thus suggesting the efficacy of oral SI supplementation.

In a small sample of young women with chronic inflammatory anemia due to *autoimmune diseases* (systemic erythematosus lupus, rheumatic fibromyalgia, connectivitis), the efficacy SI (60 mg/day, n = 9) was compared to that of FS (210 mg/day) over a 3-month course [86]. There were no differences in baseline Hb (8.5 g/dL vs. 9.0 g/dL, respectively), iron status (%TSAT, Ferritin) or inflammatory markers (CRP). Compared to FS, SI resulted in significant improvements in Hb (11.5 g/dL vs. 9.5 g/dL, respectively) and ferritin (260 ng/mL vs. 100 ng/mL, respectively). Additionally, SI, but not FS, was associated with a significant reduction in ESR and CRP levels FS [87].

Bleeding is also a common cause of anemia at the internal medicine ward, with red blood cell transfusion being the default treatment, but in many cases we could care for patients without resorting only to blood components. A recent study included 90 patients with moderate-to-severe IDA due to non-neoplastic gastrointestinal or gynecologic bleeding without inflammation and intolerant/refractory to FS [88]. Patients were randomized to receive high dose SI (120 mg/day for one month; SI group; n = 45), with or without food or antacid therapy, or IV FG (62.5 mg/day until cover total ID; FG group; n = 45). There were no differences in baseline Hb concentration (8.5 g/dL vs. 8.2 g/dL, for SI and FG groups, respectively), and both treatment were equally effective in rising Hb (12.0

g/dL vs. 12.5 g/dL, after 4 weeks, respectively) (Table 2), though treatment costs were significantly lower for oral SI (120 €/month) than for IV ferric gluconate (300 €/month). Adverse drug events were observed in 12 (26%) patients from the SI group (epigastric pain, diarrhea) and in 10 (22%) from the FG group (hypotension, urticarial, headache), but none required transfusion (Table 2). These data seem to confirm those obtained with SI supplementation in several case series and observational studies of patients with IDA of different origins (mostly bleeding) (Supplementary Material, Table S5).

In another multicenter study, 300 patients with moderate-to severe IDA (Hb < 11 g/dL, ferritin < 30 ng/mL) due to gastric (44%) or intestinal (56%) bleeding were randomized 1:1:1:1:1:1 to receive 60 mg of elemental iron daily of oral FS, microencapsulated iron (Saccarate iron), micronized ferric pyrophosphate (SunActive®), SI, heminic bisglycinated iron, or FeBIS. Patients' characteristics and follow-up time (12–24 weeks) were similar in all six groups. Compared to any other oral iron formulation tested, SI led to consistently higher Hb increments from week 6, both for the whole study population (Figure 7A) and for subgroup of patients presenting with inflammation (high CRP) (Figure 7B). At week 24, mean Hb concentrations in SI-treated patients were 13.2 g/dL for the whole, and 12.5 g/dL for the high CRP subgroup. Gastrointestinal side effect rates were low with all formulations (6–12%), except for FS (30%). Therefore, among the different oral iron formulation tested in this patient population, SI showed the faster and greater efficacy in correcting IDA, which was more evident in patients presenting with high CRP values [89].

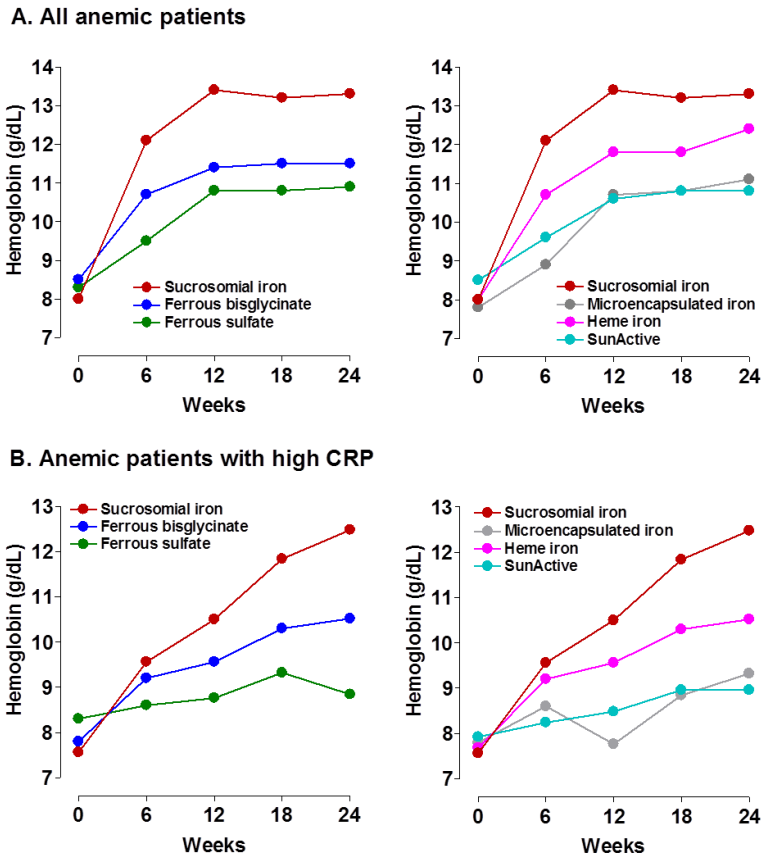

Figure 7. Comparative efficacy of different oral iron formulations for treating bleeding-induced moderate-to-severe anemia. SunActive®, micronized ferric pyrophosphate. Each oral iron formulation was tested in 60 patients (Data taken from reference [89]).

5.7. Surgery

Pre-operative anemia is frequent among patients scheduled for major elective surgery (30–40%) [13], being an independent risk factor for poor outcome (increased rates of morbidity, mortality and

readmission) and prolonged length of hospital stay [12], but enhancing the deleterious effects of blood loss and red cell transfusion. Postoperative anemia is even more frequent, affecting up to 80–90% of patients [90].

Absolute iron deficiency and iron sequestration are the leading causes of preoperative anemia (70% of cases), whereas surgery-associated blood loss and inflammation may induce and/or maintain postoperative anemia [13]. Hematinic deficiencies without anemia are also frequent and may hamper pre-operative Hb optimization and/or recovery from postoperative anemia.

As modifiable risk factors, preoperative anemia (Hb < 13 for both genders) and hematinic deficiencies should be detected, classified and treated prior to any major surgery [21]. However, the role of preoperative oral iron supplementation for treating ID, FID or IDA in these patients population has been scarcely investigated, while available evidence indicated it is not useful in the postoperative period [21,24,90].

A retrospective study evaluated the efficacy of preoperative SI in 200 paired-matched patients undergoing prosthetic hip surgery (2106) in terms of blood transfusion requirements, length of hospital stay and postoperative Hb recovery [91]. Preoperative iron supplementation with SI (30 mg/day, for 3–4 weeks preoperatively) was offered to 100 patients with Hb 12–13.5 g/dL for women or 13–14 g/dL for men, and ferritin < 100 ng/mL (ID) or ferritin > 100 ng/mL if elevated CRP or TSAT < 20% (FID). Another 100 patients with the same demographic and laboratory characteristics who did not received SI, served as control group. Compared to no iron, SI supplementation led to a reduction in the number of transfused units (0 units vs. 7 units, respectively) and the length of hospital stay (4 days vs. 6.5 days, respectively) with an estimated cost saving of 1763 €/patient. Additionally, at higher Hb levels were observed in the SI group 30 days after discharge (13.4 ± 1.5 vs. 10.2 ± 1.2, respectively). Obviously, a confirmatory randomized control trial on the beneficial effects of IS supplementation is warranted.

In this regard, the CardioSideral Heart Surgery (NCT03560687), a prospective study in 1000 consecutive patients undergoing heart surgery randomized to either SI supplementation or no treatment (control) is on-going. Its main outcome variable is reduction in transfusion rates, but changes in Hb and iron parameters, number of transfused units, postoperative quality of life (6-min walk test), tolerability and cost-effectiveness of SI will also be assessed.

Table 2. Efficacy and tolerance of oral Sucrosomial® iron in different clinical setting (9 studies, 513 patients).

Author [ref] (year) Study Type	Study Population	Treatment Compound (Dose) Duration	Baseline Hb (g/dL)	Final Hb (g/dL)	Baseline Ferritin (ng/mL)	Final Ferritin (ng/mL	Baseline TSAT (%)	Final TSAT (%)	GI Side Effects
Parisi et al. [60] (2017) RCT	80 non-anemic pregnant women 12–14 week	Control, no iron (n = 20) FS (30 mg/day) (n = 20) SI (14 mg/day) (n = 20) SI (28 mg/day) (n = 20) Up to postpartum week 6	12.0 11.9 12.0 11.9	11.6 11.8 12.0 12.0	47 44 52 53	31 43 41 50	28 27 28 27	26 27 30 29	
Mafodda et al. [51] (2017) RCT pilot	64 patients with solid tumor	SI (30 mg/day) + DEPO (500 mcg/3 weeks) FG (125 mg/wk IV) + DEPO (500 mcg/3 weeks) 2 months	9.4 9.2	12.7 12.9	---	---	---	---	3% 0%
Pisani et al. [50] (2014) RCT	99 patients with chronic kidney disease	SI (30 mg/day) (n = 66) FG (125 mg/week IV, TID: 1000 mg) (n = 33) 3 months	10.8 10.7	11.4 11.7	71 68	86 239	16.5 17.0	18.3 21.5	12% 18%
Bastida et al. [74] (2016) Case series	46 patients with inflammatory bowel disease intolerant to FS	SI (30 mg/day) 3 months	11.2	11.8 *	14.3	16.0	8.7	16.2	11%
Stuklov et al. [75] (2018) Observational	40 patients with inflammatory bowel disease	SI (60 mg/day) (n = 25) IS (100 mg/session, 500–1000 mg) (n = 15) 3 months	10.1 10.0	11.8 11.8	---	---	---	---	No
Elli et al. [48] (2016) Observational	34 patients with celiac disease	SI (30 mg/day) intolerant to FS (n = 18) FS (105 mg/day) (n = 16) 3 months	10.0 10.0	12.1 12.3	12 (all)	---	11 (all)	---	Not stated
Farinati et al. [78] (2018) Case series	20 patients with autoimmune atrophic gastritis	SI (120 mg/daily, either fasting or during meals) 8 weeks	10.5	12.5	7	27	8	18	10%
Ciudín et al. [49] (2017) Case-control	40 women after bariatric surgery	SI (28 mg/day) (n = 20) IVI (Iron sucrose 300 mg) (n = 20) 3 months	12.4 12.5	12.3 12.7	102 98	89 96	22.9 23.6	24.1 26.3	0% 0%
Giordano et al. [87] (2016) RCT	90 patient with IDA due to bleeding	SI (120 mg/day) (n = 45) FG (62.5 mg/day IV to cover TID) (n = 45) 4 weeks	8.5 8.3	12.0 12.5	5 7	---	---	---	26% 22% **

DEPO, darbepoetin; FG, ferric gluconate; FS, ferrous sulphate; GI, gastrointestinal; IBD, inflammatory bowel disease; IDA, iron deficiency anemia; IV, intravenous; PCI, percutaneous coronary intervention; RCT, randomized controlled trial; SI, Sucrosomial® iron; TID, total iron deficiency; TSAT, transferrin saturation. * Recovery from IDA: 25.7%, improvement on quality of life (EuroQoL) form 60.9 at baseline to 65.5 at the end of study period; ** Hypotension, urticaria, headache.

6. Efficacy of Sucrosomial® Iron: An Overview

Most relevant evidence on the bioavailability, tolerability and efficacy of oral SI in different preclinical and clinical settings has been presented as lectures or communication to the 3rd, 4th, 5th and 6th International Multidisciplinary Courses on Iron Anemia and other international meetings. However, a growing number of studies have been already published as full peer-review papers [40,42,47–51,60,69,85,91]. Characteristics and results for a number of clinical studies are summarized in Table 2.

Preclinical studies clearly demonstrated that SI has unique structural, physicochemical and pharmacokinetic characteristics. The presence of sucrester confers gastro-resistance to SI, protects its trivalent pyrophosphate iron against enzymatic reduction, and promotes its absorption across the intestinal epithelium, by a DMT-1 independent pathway, greatly mediated by M cells. All this enables oral SI to have a high iron bioavailability and a low gastrointestinal toxicity.

The analysis of available clinical evidence seems to support oral SI as a new valid opportunity for iron supplementation, which is more comfortable and efficacious (lower doses, higher Hb increments and/or better replenishment of iron stores) and has a better tolerability than traditional oral iron salts (Table 2). Sucrosomial® iron has been also demonstrated to have similar effectiveness, with lower risks, in clinical settings where IV iron was the usual treatment option (e.g., CKD, cancer, bariatric surgery, etc.) (Table 2).

Thus, administration of oral SI emerges as a most valuable first option for treating uncomplicated iron deficiency, and even more for subjects with intolerance or lack of efficacy from other iron salts. Moreover, oral SI should be also considered as an alternative to IV iron for initial and/or maintenance treatment in different patient populations. Nevertheless, appropriately sized randomized control trials are needed to confirm the promising results obtained with oral SI supplementation in different clinical settings.

Supplementary Materials: The following are available online at www.mdpi.com/link, Table S1: Sucrosomial® iron (SI) administration in oncologic patients (10 studies, 241 patients), Table S2: Sucrosomial® iron (SI) administration in patients with chronic kidney disease (CKD) (11 studies, 294 patients), Table S3: Sucrosomial® iron (SI) administration in patients with gastrointestinal disease (7 studies, 122 patients), Table S4: Sucrosomial® iron (SI) administration in cardiology patients (8 studies, 161 patients), Table S5: Sucrosomial® iron (SI) administration in Internal Medicine (10 studies, 236 patients).

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Abbreviations

AAG, autoimmune atrophic gastritis; ACI, anemia of chronic inflammation; AntiH2, histamine H2 receptor antagonists; AUC, area under the curve; BPDS, bathophenanthroline disulfonic acid; CACO2, human colon cancer cell line; CD, celiac disease; CHF, congestive heart failure; CIA, chemotherapy-induced anemia; CKD, chronic kidney disease; Cmax, maximal plasma concentration; CRP, C-reactive protein; DEPO, darbepoetin;

DMT-1, divalent metal transporter-1; DSS, dextran sodium sulfate; ESA, erythropoiesis stimulating agent; FCM, ferric carboxymaltose; FeASC, ferrous ascorbate; FeBIS, ferrous bisglycinate; FeDEX, iron dextran; FeEDTA, ferrous ethylene-diamine-tetra-acetate; FePYR, ferric pyrophosphate; FG, ferric gluconate; FI, ferrous iron; FID, functional iron deficiency; FS, ferrous sulfate; FXT, ferumoxytol;GI, gastrointestinal; Hb, hemoglobin; HD-CKD, hemodialysis-dependent CKD; IBD, inflammatory bowel disease; ID, iron deficiency; IDA, iron deficiency anemia; IRIDA, iron-refractory iron deficiency anaemia; IS, iron sucrose; ISM, iron isomaltoside 1000; IV, intravenous; LMWID, low molecular weight iron dextran; M cell, microfold cell of Peyer's patches (RajiB cell); MCH, mean corpuscular hemoglobin; MCV, mean corpuscular volume; MSD, myelodysplasia; NCGS, non-celiac gluten sensitivity; ND-CKD, CKD non on dialysis; PCI, percutaneous coronary intervention; PPI, proton pump inhibitors; RCT, randomized controlled trial; SI, Sucrosomial® iron; Socs3, suppressor of cytokine signaling 3; TID, total iron deficiency; TSAT, transferrin saturation; VAS, visual analog scale; WHO, World Health Organization.

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Table S1. Sucrosomial iron (SI) administration in oncologic patients (10 studies, 241 patients)

Author (year) [ref] Study type	Patients	Treatment Compound (Dose) Duration	Baseline Hb (g/dL)	Final Hb (g/dL)	Baseline Ferritin (ng/mL)	Final Ferritin (ng/mL	Baseline TSAT (%)	Final TSAT (%)	GI side effects
Renso et al (2015) [1] Case series	12 patients with lymphoproliferati-ve disease	SI (30 mg/day) +DEPO 150 mcg/w Chemotherapy 2 months	10.1	10.9	---	---	---	----	4%
Petrungaro et al. (2015) [2] Case series	10 patients with lymphoma (4 HL,6NHL)	SI (30 mg/day) After chemotherapy 2 months	10.0	11.2 (↑QoL)	43	93	---	---	---
Grillone et al. (2016) [3] Case series	30 patients with solid tumors	SI (30 mg/day) Chemotherapy 2 months*	11.2	11.3					10%
Romano et al. (2016) [4] Case series	25 Hodgkin lymphoma ≥2B	SI (30 mg/day) Chemotherapy End of treatment**	10.2	12.8	90	277	14.3	35.9	No
Barni et al. (2017) [5] Case series	16 patients with solid tumor	SI (30 mg/day) Palliative chemotherapy 3 months**	11.2	10.9	---	---	13.5	20.6	No
Sabbatini et al (2017) [6] Case series	30 patients wih solid tumors	SI (30 mg/day) (n=15) SI (60 mg/day) (n=15) 3 months**	10.5 9.8	12.0 12.0	---	---	---	---	Some dyspepsia and diarrhea
Poyato et al. (2017) [7] Case series	9 patients with solid tumors	SI (30 mg/day) Chemotherapy 2 months***	9.8	10.7	---	---	---	---	11%
Monari et al (2016) [8] Observational	15 Advanced prostate cancer with bone metastases	SI (30mg/day) (n=7) No iron (n=8) Chemo-radiotherapy 6 months	11.1 10.9	12.2 9.7	---	---	---	---	-- Well tolerated
Barragans et al. (2016) [9] RCT pilot	15 patients with peritoneal carcinomatosis	SI (30mg/day) (n=8) FS (80 mg/day) (n=7) 3 months	10.4 9.5	12.5 11.9	529 1048	---	10 8	---	25% mild 29% mild
Barzaghi et al. (2016) [10] Observational	15 patients advanced rectal cancer & bleeding	SI (30 mg/day) (n=11) FH (?)+folic acid 14 days	8.0	11.6 11.4	100	---	25	---	No

*2 patients started ESA; **No ESA or blood transfusion during study period, 70% reached delta Hb ≥2 g/dL or Hb ≥12 g/dL; *** one patient transfused. DEPO, darbepoetin; ESA, erythropoiesis stimulating agent; FH, ferrum Haussman?; GI, gastrointestinal; QoL, quality of life; TSAT, transferrin saturation.

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Table S2. Sucrosomial iron (SI) administration in patients with chronic kidney disease (CKD) (11 studies, 294 patients)

Author (year) [Ref] Study type	Patients	Treatment Compound (Dose) Duration	Baseline Hb (g/dL)	Final Hb (g/dL)	Baseline Ferritin (ng/mL)	Final Ferritin (ng/mL	Baseline TSAT (%)	Final TSAT (%)	GI side effects
Cuzzola et al. (2016) [1] Case series	35 ND-CKD Intolerant to FS	SI (30 mg/day)? 3 months	9.3	11.1	---	---	11.2	8.9	No
Dimokvic et al. (2016) [2] Case series	31 ND-CKD3-4	SI (30 mg/day) ESA (no change in dosage) 6 months	10.2	10.3	213	169	26.8	24.4	Mild*
Arenas et al. (2016) [3] Case series	24 ND-CKD3-4	SI (30 mg/day) 6 months	11.1	12.8	34	75	13.8	26.1	No
Arrizabalaga et al. (2017) [4] Case series	31 ND-CKD3 71% intolerant to conventional oral iron	SI (30 mg/day) 12 months	12.0	11.9	100	116	17.0	18.7	3%
Griveas et al. (2017) [5] Case series	30 ND-CKD3-5	SI (30 mg/day)? 18 months	11.0	11.9	43	99	---	---	No
Griveas et al. (2018) [6] Case series	40 ND-CKD3-5	SI (30 mg/day)? 24 months	11.6	12.0	74	66	---	---	No
Equitani et al. (2016) [7] Observational	16 ND-CKD Severe anemia	SI (60mg/day)+ ESA (n=8) No iron + ESA (n=8) 3 months	8.6 8.9	12.6 11.4	12 21	68 21	24 28	39 19	NO
Moussa-Abdi et al (2015) [8] Observational	28 ND-CKD	SI (60/mg/day) (n=14) FS (100 mg/day) (n=14) 3 months	11.2 11.3	11.7 11.4	78 182	90 228	17.9 22.3	22.4 31.8	14% 58%
Panichi et al.[#] (2015) [9] RCT	12 HD-CKD	SI (30-180 mg/week) FG (30-180 mg/week) 3 months	12.7 12.0	12.7 12.6	--- ---	--- ---	24.0 27.6	21.0 30.8	No
Pistoni et al. (2016) [10] RCT?	22 HD-CKD	SI (360 mg/week)+ESA (n=13)** FG (16-190 mg/week)+ESA (n=9)*** 3 months	10.7 11.1	11.4 11.4	312 285	177 250	21.6 18.6	20 15.7	---
Cucchiari et al. (2018) [11] Case series	25 HD-CKD	SI (90 mg/week) 3 months All patients were previously receiving IV ferric gluconate (62.5 mg/week)	11.2	11.0	226	97	30	16	No

ND, not on dialysis; HD, hemodialysis; FG, ferric gluconate; ESA, erythropoiesis stimulating agent; EPO, erythropoietin; TSAT, transferrin saturation index; GI, gastro-intestinal.
*More frequently mild dyspeptic symptom and less frequently constipation. [#]Need for EPO 36% with SI vs. 57% with FG. **EPO dose decreased by 2000 IU/week in 38% and increased in 23% of SI patients. ***EPO dose increased by 2000 IU/week in 67% and decreased in 11% of FG patients.

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Table S3. Sucrosomial iron (SI) administration in patients with gastrointestinal disease (7 studies, 122 patients)

Author (year) [Ref] Study type	Patients	Treatment Compound (Dose) Duration	Baseline Hb (g/dL)	Final Hb (g/dL)	Baseline Ferritin (ng/mL)	Final Ferritin (ng/mL	Baseline TSAT (%)	Final TSAT (%)	GI side effects
Inflammatory Bowel Disease (IBD)									
Scarpulla et al. (2016) [1] Case series	10 IBD	SI (30 mg/day) 2 months	10.5	12.3	≤200	---	≤20	---	No
Stuhlov et al (2017) [2] Case series	6 IBD	SI (60 mg/day) 3 months	11.1	12.4	12.4	20.2	8.1	15.7	No
Indriolo et al. (2014) [3] Observational	27 IBD	SI (30 mg/day) (n=7) FS (105 mg/day) (n=8) No iron (n=11) 3 months	10.6 10.9 11.4	12.6 12.3 11.9	---	---	---	---	7.1% 12.5%
Romano et al. (2016) [4] Observational	12 IBD	SI (60 mg/day) (n=6) FS (210 mg/day) (n=6) 2 months	8.0 8.0	11.5 9.5	5 6	15 9	---	---	50% mild 100%
Celiac disease /gluten-sensitivity									
Ragozzino et al (2015) [5] Case series	6 Celiac disease 28 Non-celiac gluten sensitivity	SI (30 mg/day 15d, 15 mg/day 75d) 3 months	8.8 9.7	11.5 12.5	13 18	23 29	---	---	---
Scorsone et al. (2015) [6] Observational	24 Celiac disease All T1DM	SI (30 mg/day) (n=12) FS (105 mg/day) (n=12) 1 month	? ?	+1.27 +0.82	---	---	19.1 17.4	23.6 18.7	---
Bariatric surgery									
Badiali et al (2017) [7] Case series	9 Bariatric surgery RYGBP	SI (30-60 mg/day) 3 months	11.4	12.6	6.7	19.0	---	---	No

FS, ferrous sulphate; GI, gastro-intestinal; IS, IV iron sucrose; TSAT, transferrin saturation index; T1DM, type 1 diabetes mellitus

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Table S4. Sucrosomial iron (SI) administration in cardiology patients (8 studies, 161 patients)

Author (year)[Ref] Study type	Patients	Treatment Compound (Dose) Duration	Baseline Hb (g/dL)	Final Hb (g/dL)	Baseline Ferritin (ng/mL)	Final Ferritin (ng/mL	Baseline TSAT (%)	Final TSAT (%)	GI side effects
Congestive heart failure									
Marazia et al (2017)[1] Case series	9 patients with CHF-LVDF (EF ≤39%)	SI (60 mg/day) * 1 month	10.3	11.0	32	67	---	----	---
Putorti et al. (2017)[2] Case series	10 patients with Hypertensive heart disease	SI (60 mg/day) 5 weeks	10.5	11.5	---	---	---	---	No
Karavidas et al. (2017)[3] Case series	10 patients with CHF-LVDF (EF ≤39%)	SI (30 mg/day)** 3 months	12.8	13.4	48	102	---	---	No
Cardiac surgery									
Testa et al. (2017)[4] Case series	28 patients after cardiac surgery	SI (30 mg/day, months 1 and 3)*** 3 months	10.0	11.9	334	63	---	---	No?
Grossi et al. (2017)[5] Case series	16 patients after cardiac surgery	SI (120 mg/day, 7 days) SI (60 mg/day, 14 days) 2-3 weeks[#]	9.7 10.0	10.2 11.0	---	---	---	---	No
Buioni et al. (2017)[6] Case series	22 patients after cardiac surgery	SI (120 mg/day) 3 weeks	10.0	12	---	---	---	---	No
Other interventions									
Ruperto et al. (2017)[7] Observational	50 patients percutaneous coronary intervention	SI (30 mg/day) (n=25) FS (105 mg/day) (n=25) 3 months post-PCI	8.9 9.1	11.2 11.0	---	---	---	---	0% 32%
Pagliani et al. (2017)[8] Observational	16 patients in cardiac rehabilitation	SI (60 -120 mg/day) (n=8) FS (105 mg/day) (n=8) 14 days	9.5 9.2	10.1 9.9	500 600	400 870	---	---	0% 33%

*BNP and CRP decreased with treatment; **BNP and CRP decreased with treatment, 6MWD increased after treatment, and NYHA improved; ***BNP and CRP decreased with treatment, 6MWD increased after treatment; [#]6MWD increased after treatment.

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Table S5. Sucrosomial iron (SI) administration in Internal Medicine (10 studies, 236 patients)

Author (year)[Ref] Study type	Patients	Treatment Compound (Dose) Duration	Baseline Hb (g/dL)	Final Hb (g/dL)	Baseline Ferritin (ng/mL)	Final Ferritin (ng/mL	Baseline TSAT (%)	Final TSAT (%)	GI side effects
Alimenti et al (2015)[1] Case series	30 IDA various origin	SI (30 mg/day)? 2month	10.2	??	---	---	---	---	10%
Campanella et al (2015)[2] Case series	16 IDA various origin	SI (30 mg/day) 40 days SI (30 mg/day) 60 days	10.0 10.8	11.9 12.6	<20 <20	----	----	---	No
Scifo et al (2015)[3] Case series	9 hemorrhoidal disease with IDA	SI (60 mg/day) 3 month	9.4	10.8	10	80	18	34	No
Vallerio et al (2016)[4] Case series	8 HVC-related cirrhosis	SI (60 mg/day)* 1 month	9.4	10.1	10	36	19	24	10%
Nasuti et al (2016)[5] Case series	30 IDA various origin	SI (60 mg/day) 2 month	9.8	12.1	---	---	---	---	10%
Nadir et al (2017)[6] Case series	4 IDA because of bleeding	SI (300 mg/day, 10 days + 120 mg/day, 50 days) 2 month	9.0	12.5	14.5	103	---	---	No
Svanera et al (2017)[7] Case series	3 IDA various origin	SI (30 mg/day) 4 month	7.3	11.3	1.6	87	---	---	No
Berardi et al. (2015)[8] RCT pilot	20 MDS with refractory anemia	SI (14mg/day) + EPO 40,000 IU/week (n=10) No iron + EPO 40,000 IU/week (n=10) 3 months	8.8 9.0	12.5 11.5	---	---	<20 <20	---	No
Parisi et al. (2016)[9] Observational	34 patients with systemic sclerosis	SI (60 mg/day) (n=21)** FS (105 mg/day) (n=22) 3 months	10.2 10.7	13.4 11.9	130 110	240 150	---	---	0% 23%
Bellodi et al. (2016)[10] Observational	82 patients with IDA	SI (30 mg/day) FG or FCM (500 mg) + SI (30 mg/day) 6-7 months	10.3 8.8	11.6 12.2	7.5 5	27.5 27	---	---	3.7%

EPO, recombinant erythropoietin; FCM, ferric carboxymaltose; FG, ferric gluconate; FS, ferrous sulphate; GI, gastrointestinal; Hb, haemoglobin; IDA, iron deficiency anaemia; TSAT, transferrin saturation.

*Reduction of aortic stiffness. ** SI treatment reduced ESR and CRP levels.

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