Chapter

FERALGINE™ a New Oral iron Compound

Valentina Talarico, Laura Giancotti, Giuseppe Antonio Mazza, Santina Marrazzo, Roberto Miniero and Marco Bertini

Abstract

Management of iron deficiency (ID) and iron deficiency anemia (IDA) is primarily focused to remove, when possible, the underlying cause of ID; subsequently its treatment is primary focused on iron stores repletion. Ferrous sulphate (FS) remains the mainstay of treatment and it is recommended as the first-line treatment of ID and IDA in children as in adults by all guidelines of scientific societies. However the effectiveness of FS is largely compromised by increased adverse effects, poor compliance and discontinuation of treatment. A new oral iron source named FERALGINE™ (FBC-A) has been recently developed. This new molecule is a patented co-processed one-to-one ratio compound between Ferrous Bysglicinate Chelate (FBC) and Sodium Alginate (AA), obtained by using a spray drying technology. The data presented in this short review highlight the efficacy and safety of the treatment with FBC-A and support its use in adult patients with IDA. Furthermore the present review also provides preliminary evidence to suggest FBC-A as first-line treatment for ID/IDA in patients with celiac disease (CD) or inflammatory bowel diseases (IBD).

Keywords: Iron deficiency, Iron deficiency anemia, oral treatment, compliance

1. Introduction

Iron deficiency (ID) is the most common nutritional deficiency worldwide, heavily concentrated in several regions including Asia, Latin America and Africa, where it may affect up to 60% of the entire population. In countries with high development rate prevalence of iron deficiency anemia (IDA) is estimated at 9% and accounts approximately for 50% of all anemia cases, representing a frequent medical condition encountered in clinical practice by general practitioners, pediatricians and several other specialists. In these countries the prevalence of ID/IDA is higher in pediatric age, especially in two life phases: one that occurs between the first and third year of life (2.3–15%) and another in adolescence (3.5–13% in males, 11–33% in females). In adults its prevalence is less than 1% in men <50 years of age, 2–4% in men >50 years of age, 9–20% in menstruating teenagers and young women, and 5 to 7% in postmenopausal women. In people older than 65 years its prevalence is 12%. World Health Organization (WHO) data show that ID/IDA in pregnancy is a significant problem

throughout the world with a prevalence ranging from an average of 14% of pregnant women in industrialized countries to an average of 56% (range 35–75%) in developing countries [1–5].

The most frequent etiologic factors in ID/IDA are decrease iron intake, impaired iron absorption, increase iron loss and increased iron requirements. In adult females increased menstrual flows and reduced iron absorption, as occurs in celiac disease (CD), are the most common mechanisms of ID/IDA. Vegetarians, especially vegans, obese individuals, blood donors and competitive endurance athletes represent populations at risk of ID/IDA. In children increased daily requirement and CD are the leading causes of ID/IDA [1–5].

Iron (Fe) is an essential trace mineral naturally present in many foods, but it is also available as a dietary supplement. In the typical western diet iron is mainly (85–90%) present as inorganic form Fe2+ (ferrous) and Fe3+ (ferric), the remaining amount as heme form. The diet contains up to 20 mg of daily iron intake of which 1–2 mg are absorbed. Fe3+ is less bioavailable as it has to be converted into Fe2+ in order to be absorbed. The absorption of Fe2+ primarily occurs in the proximal duodenum, at the brush border of the mucosa cells, through a membrane transport protein called Divalent Metal Transporter 1 (DMT1). This process is regulated by the cytochrome B (DCYTB), a ferric reductase located on the apical membrane of duodenal enterocytes. Otherwise heme-iron is absorbed in the same bowel district, but separately from DMT1 and more efficiently than inorganic Fe [1–5].

Management of ID/IDA is primarily aimed at removing, whenever possible, the underlying cause of ID. Subsequently iron replacement is always indicated to replete iron stores. The use of oral iron formulations is the current standard treatment; however in certain situations discussion remain open if the intravenous iron might be a more suitable modality for iron supplementation [1–5].

Ferrous sulphate (FS) remains the mainstay of treatment since it was first introduced in 1832 by the French physician Pierre Blaud (*Blaud's pills*) and it is recommended as the first-line treatment of ID/IDA in children and in adults by all guidelines of scientific societies. Two other bivalent iron preparations are primary suggested: ferrous gluconate and ferrous fumarate. None of these compounds seem to be better than the others [1–5].

The optimal oral iron dose of FS is yet to be established. Traditionally recommended dose in children is 2–6 mg/kg/day in term of elemental iron [5]. In adolescents and adults recommended dose is 50–200 mg once daily or in divide doses [1–4]. The optimum frequency of oral supplementation is still uncertain. It has been demonstrated that one day treatment saturates the intestinal absorption processes. According to more recent data of the literature the administration of iron on every other day might be equal or more effective than daily doses with less side effects [2, 4, 6]. When therapy is fully effective the anticipated increase in hemoglobin levels occur after 2 to 3 weeks (increase by 1–2 g/dl within 1 month) of iron treatment, and reaches normal levels by 2–3 months. When the hemoglobin levels have been corrected, treatment should be continued for 3–4 months in order to completely fill the body's iron stores [1–5].

Ferrous sulphate absorption ranges between 5–28% at the fastest. During oral iron therapy non-absorbed iron is potentially toxic for the gastrointestinal mucosa due to its oxidative properties leading to occurrence of gastro-intestinal adverse events. Nausea, vomiting, diarrhea or constipation, epigastric discomfort and colicky pain often represent a limit for patient domiciliary compliance decreasing the adherence to protocols with consequent failure of therapy efficacy. Actually many patients (20–70%)

experience some type of gastrointestinal discomfort during oral iron salts intake, jeopardizing the prolonged (several months) planned treatment [1–7]: up to 40% of patients may self-discontinue the medication without discussing with medical doctor [8]. It is not surprising that effectiveness of oral iron is largely compromised by lack of absorption, poor compliance, increased adverse effects and discontinuation of treatment.

In order to improve tolerability several formulations with Fe2+ or Fe3+ have been proposed by pharmaceutical laboratories during the last decades. Generally these oral iron compounds are better tolerated than FS but may be less effective in iron replacement, ferrous compounds remaining anyway more absorbed than trivalent ones. However, often these preparations have the common drawback of being less effective in malabsorptive disorders [1–7]. Clinical studies concerning these new compounds remain limited while rigorously randomized designed clinicaltrials are often lacking.

Iron amino acid chelates represent a source of iron which has proven to be highly bioavailable with decreased extent gastrointestinal adverse effects when compared to FS [9]. Ferrous Bisglycinate Chelate (FBC) is the most studied compound among these new formulations. In FBC one molecule of ferrous iron is chelated by two molecules of glycine resulting in two heterocyclic rings. Several clinical trials showed clinical bioequivalence between this source of iron at low dosage and FS at standard doses with ratio 1 to 4 [10–12]. Unfortunately, during treatment with FBC, albeit very rare, some gastro-intestinal adverse effects can occur. Another limit of FBC could be represented by "the iron taste" of the preparation that might worsen patient compliance.

To ameliorate its bioavailability, taste and tolerability, a new oral iron source named FERALGINE™ (FBC-A) has been recently developed [13, 14]. This new molecule is a patented co-processed one-to-one ratio compound between FBC and Sodium Alginate (AA), obtainedby using a spray drying technology [15, 16]. AA as well as FBC has been recognized as GRAS by FDA [17].

Sodium Alginate has usually been used as "gastro-protection". It is a non-toxic, biocompatible, biodegradable polymer, which belongs to the polysaccharides naturally present in seaweed. The contact between AA and the acidic environment in the stomach leads to the formation of a gel layer that hasa protective effect on the mucosa membranes of the stomach and esophagus. For this reason AA is an ingredient of many medications (antacids) commonly used in the treatment of heartburn and reflux diseases [18, 19]. Mucoadhesive microsphere of AA have recently demonstrated to be a unique "carrier system" for many pharmaceuticals preparation increasing not only oral iron but also other drugs bioavailability such as metformin, amoxicillin, furosemide, ibuprofen, insulin, acyclovir, captopril, glipizide, dicumarol. This "carrier system" results really in a promising and cost-effective method drug delivery system to improve oral bioavailability and to reduce gastrointestinal drugs side effects [20–22]. Spray drying is one of the most powerful technological process for the pharmaceutical industry << being an ideal process where the moisture content, bulk density and morphology end-product must comply with precise quality standards regarding particle size distribution, residual moisture content, bulk density and morphology>> [15, 16, 23–25]. (**Figure 1**) Spray drying technology comes of age during World War II, with the sudden need to reduce the transport weight of foods and other materials. This technique enables the transformation of feed from a fluid state into dried particulate form by spraying the feed into a hot drying medium. It is a continuous particle processing drying operation. As well described by Gervasi et al. < <spray drying process mainly involves five steps: 1) Concentration: feedstock is normally concentrated prior to introduction into the spray dryer; 2) Atomization: the atomization stage creates the optimum condition for evaporation to a dried product

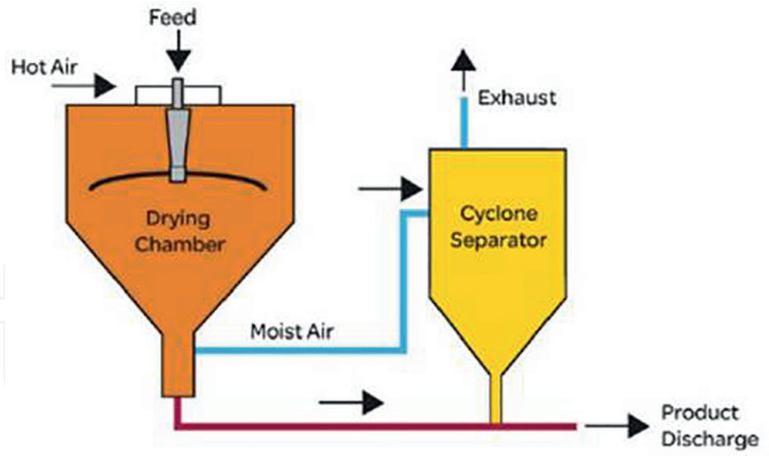

Figure 1.
Spray drying system.

having the desired characteristic; 3) Droplet-air contact: in the chamber, atomized liquids brought into contact with hot gas, resulting in evaporation of 95% of the water contained in the droplets in a matter of a few minutes; 4) Droplet drying: moisture evaporation takes place in two stages: during the first stage, there is sufficient moisture in the drop to replace the liquid evaporated at the surface and evaporation takes place at a relatively constant rate and the second stage begins when there is no longer enough moisture to maintain saturated conditions at the droplet surface, causing a dried shell to form at the surface. Evaporation then depends on the diffusion of moisture through the shell, which is increasing in thickness; 5) Separation: cyclones, bag filter, and electrostatic precipitators may be used for the final separation stage>> [14].

In FBC-A, since FBC and AA are present in 1 to 1 ratio, every little particle of the powder has the same morphology and quantity of the two different co-processed substances. The new "co-processed compound", obtained by spray drying technology, confers to the iron powder an increased and uniform superficial area and, consequently, quick and more extensive iron absorption together with an increased gastrointestinal protection (**Figure 2**). In the same time, the uniform presence of AA in this

Figure 2.
FBC-A powder (picture making by stereomicroscopy Wild Heerbrugg Makroskop M420 linked to an OPTIKAM MICROSCOPY DIGITAL USB CAMERA) [14].

product, allows theFBC to be released more constantly and slowly when confronted to FBC alone and let the DMT1 receptors to better uptake iron. DMT1 receptor saturation could be a limit in oral iron bioavailability that could be exceeded by FBC-A. In fact, slowly availability of iron by FBC-A administration could result in DMT-1 unsaturation with the consequence of increasing iron bioavailability [13, 14, 23–25].

2. Clinical studies

Preliminary clinical trials confirm the bioavailable of FBC-A whiles the "dispert effect" of AA on FBC accounts for the good tolerability at gastro-enteric levels. FBC-A also improves iron taste when compared to FBC alone, increasing patient's compliance.

Ame et al. studied 12 patients (9 women and 3 men with medium age of 63.83 ± 20.94 years) affected by IDA (4 patients present multifactorial anemia, 2 hypermenorrhea-related anemia, 2 cancer-related anemia, 2 increased-iron loss anemia, 1 post transplantation anemia and1 hypo-regenerative anemia), enrolled in an open prospective uncontrolled pivotal clinical trial. Mean hemoglobin (Hb) levels at the beginning of study (T0) were 10.49 g/dl (range 7.8–11.9 g/dl), mean serum iron values were 27,9 μg/dL (range 13–39 μg/dL) and mean serum ferritin (SF) values were 26 μg/ml (range 4–89 μg/ml). The patients presented history of chronic fatigue and/or asthenia at enrolment. All patients received FBC-A (30 mg of elemental iron) once a day for a period lasting from 35 days to 60 days (mean 46.25 days). At the end of treatment (T1) mean Hb values were 11.6 g/dl (range 8.9–13.9 g/dl), mean serum iron values were 48.9 mg/ld. (range 34–68 mg/dl) and mean SF values were 35 μg/ml (range 9–94 μg/ml), ($p < 0.0001$) (**Figure 3**). No FBC-A adverse events or therapy interruption were reported during the trial. Significant as a small quantity of elemental iron (30 mg daily) has been able to increase the Hb as required by international guidelines (1 g/dl.Hb/month) confirming the high bioavailability ofthis new compound. Subject performances ameliorated significantly in all patients [26].

Celiac disease (CD) is an immunologically-mediated disorder characterized by duodenal mucosa villi atrophy. As iron is primarily absorbed at duodenum level, iron absorption is reduced in celiac patients. In fact, the most frequent extra-intestinal manifestation of CD is IDA, with a prevalence between 12 and 82% in patients with new CD diagnosis. Absorption of FS and other iron formulationsis limited in patients with undiagnosed and active CD. Iron supplementation generally results less effective in these patients leading to a form of refractory IDA. The effectiveness of iron administration may be reduced also during the first months of gluten-free diet (GFD), when

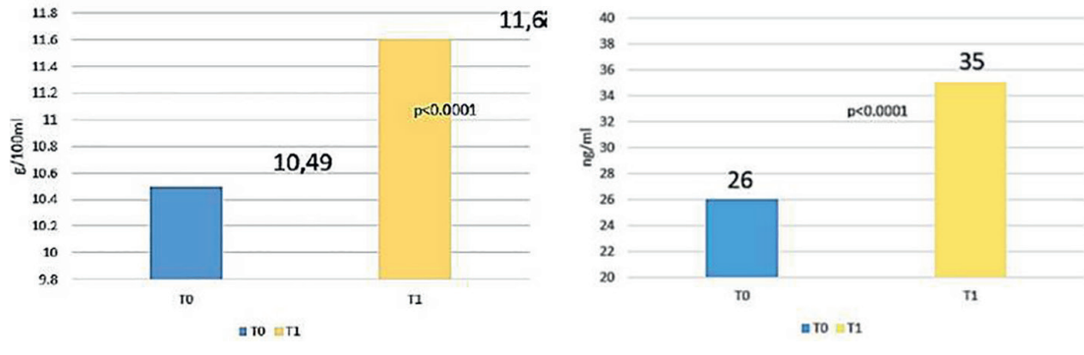

Figure 3.
Increase in mean Hb and SF levels from time To to T1 after administration of FBC-A [26].

the mucosa healing is yet on-going. Furthermore a poor iron compoundstolerabilityis particularly frequent in patients with CD, decreasing patient's compliance. These events increase the risk of making every kind of oral iron treatment unhelpful [27, 28].

The oral iron absorption test (OIAT) is an old screening test to assess iron absorption. Forgotten for many years it has been recently re-evaluated in clinical practice [29, 30]. The test consists of measuring plasma iron increase in the next hours after a single dose of an oral iron preparation. It has been demonstrated that this increment reflects the real capacity of iron absorption from the gastrointestinal tract [29, 30]. In a previous study we tested FBC by OIAT in pediatric patients affected by overt CD (disease at diagnosis before starting GFD) or on GFD, showing as FBC was well absorbed in spite of duodenal mucosal lesions [31].

More recently Giancotti et al. studied 26 patients with IDA of which 14 were also affected by overt CD (mean age: 32.28 years) and 12 were not affected (mean age: 33.58 years) [32]. The demographic and laboratory baseline parameters of the patients are summarized in **Table 1.**

An OIAT was performed in each patient by administrating FBC-A (60 milligrams of elemental iron). Serum iron was evaluated at baseline (T0) and after 2 h (T1) from the iron ingestion. The OIAT was well tolerated in all patients. There was a clear improvement in iron serum in all patients (T0 = 31.30 μg/dL vs. T1 = 105.3 μg/dL # $p < 0.0001$). The relationship between the severity of IDA and the absorption of iron showed that patients with severe anemia (Hb < 10 g/dL) had an higher increase in serum iron after the OIAT (about nine times) compared to patients with mild/moderate forms of anemia (TO 12.00 μg/dL and 35.76 μg/dL *vs* T1 109.20 μg/dL and 104.66 μg/dL in severe anemia and mild/moderate anemia, respectively). Surprisingly, an equivalent improvement in serum iron occurred in the two groups of patients (IDA plus CD and IDA without CD): T0 = 28.21 μg/dl *vs*. T1 = 94.14 μg/dl, ($p = 0.004$) in the first group (Group A) and T0 = 34.91 μg/dl *vs*. T1 = 118.83 μg/dl ($p = 0.0003$), in the other group (Group B) respectively as shown in **Figure 4** [32]. All the 26 patients were compliant to the treatment with FBC-A (60 milligrams of elemental iron once a day) and continued it until normalization of Hb levels and SF that occurred after 3 and 5 months. Response to treatment was monitored with periodical evaluation of Hb, serum iron, transferrin saturation and SF (unpublished personal data).

These results clearly demonstrated that FBC-A is well tolerated and well absorbed, not only in anemic non-celiac patients but also in patients with overt CD. Furthermore as it is widely assumed that side effects limit compliance to iron oral treatment, these results confirm that FBC-A is very promising for treatment of iron deficiency also in patients affected by CD.

Talarico et al. referred a 22-year-old girl with IDA resistant to FS therapy who was finally diagnosed as a celiac patient with multiple duodenal biopsies. A strictly GFD was then prescribed and in order to evaluate the absorption of a different iron compound, an OIAT was performed with FBC-A at the dosage of 30 mg of elemental iron. The results confirmed a good iron absorption as the serum iron increased from 27 μg/dl at

	Males	Females	Hb ± SD (g/dl)	Serum ferritin±SD (ng/dl)	Serum iron ±SD μg/dL)
Celiac-IDA	2	12	11.07 ± 1.04	10.44 ± 15.9	28.21 ± 14.9
Non-celiac IDA	0	12	10.80 ± 0.9	12.30 ± 13.8	34.91 ± 23.2

Table 1.
The demographic and laboratory baseline parameters of the patients [32].

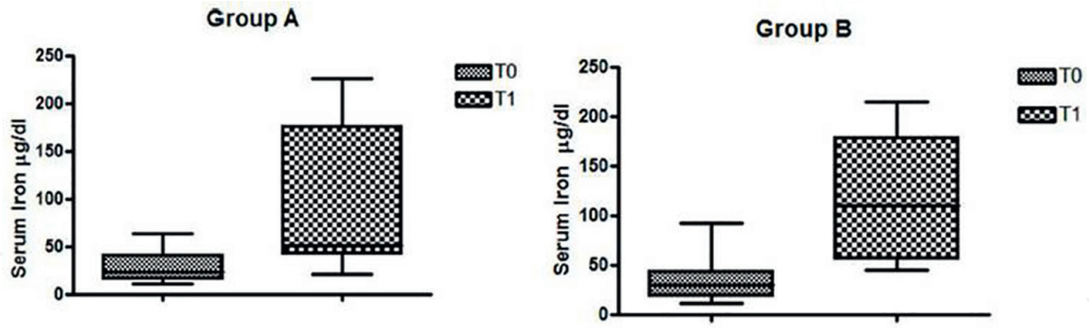

Figure 4.
Change in serum iron levels in patient with IDA and CD (group A) and without CD (group B) after OIAT [32].

baseline (T0) to 93.2 µg/dl after two hours (T1). Then, treatment with FBC-A at a dosage of 30 mg/day was promptly started. A general status recovery was observed in a few days. After 3 months Hb reached 11.5 g/dl; after 6 months iron stores were replaced (SF 50 ng/dl). CD serology normalized after one year, with complete resolution of anemia and gastrointestinal symptoms [33]. This case report confirms the efficacy of FBC-A in patients with overt CD, being already well absorbed during the first months of GFD.

Rondinelli et al. performed an OIAT study after oral ingestion of FBC-A (60 mg of elemental iron) on 14 patients (8 females and 6 males) with IDA (mean age 55.28 ± 8.17 years). The mean Hb level was 9.7 g/dl (range 8.7–10.7g/dl) and mean SF level was 8.23 ng/ml (4–12 ng/ml). At baseline time (T0) mean plasma iron was 11.21 µg/dl ± 10.66. Two hours after taking FBC-Ain fasting condition (T2) mean plasma iron increased significantly to 111.00 µg/dl ± 51.56 ($p < 0.00001$) (**Figure 5**) [34].

The increase of serum iron was greater than that observed after administration of bivalent iron by others authors (**Figure 6**).

Crohn's disease and ulcerative colitis are the two expressions of the Inflammatory Bowel Disease (IBD), a complex of immunologically mediated diseases due to a dysregulated immune response to commensal flora in a genetically susceptible host. Among IBD patients, IDA is more frequent than in general population, due to multifactorial reasons including chronically inflammation, blood loss and low iron absorption. Goodhand et al. showed as children (88%) and adolescents (83%) were more often

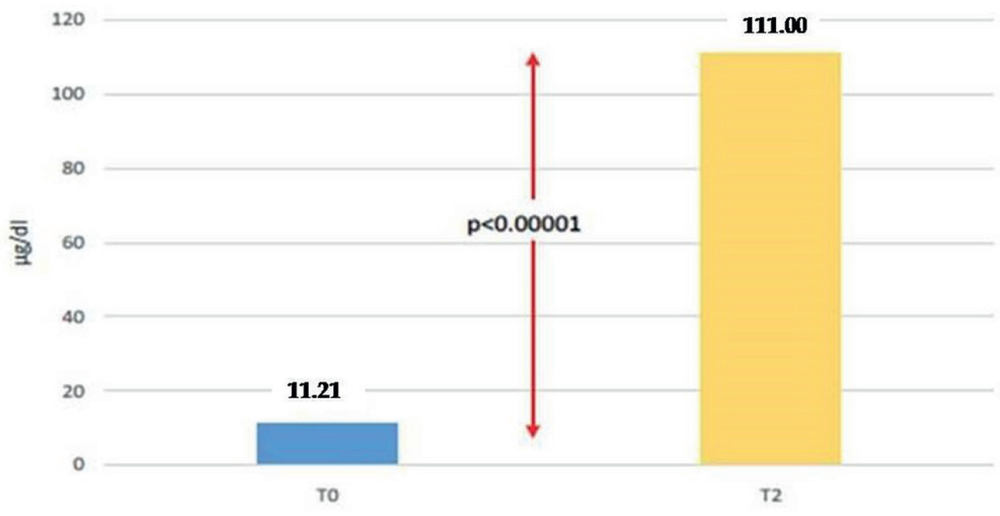

Figure 5.
OIAT: plasma iron before (TO) and after 2 hours (T2) from 60 mg of FBC-A [34].

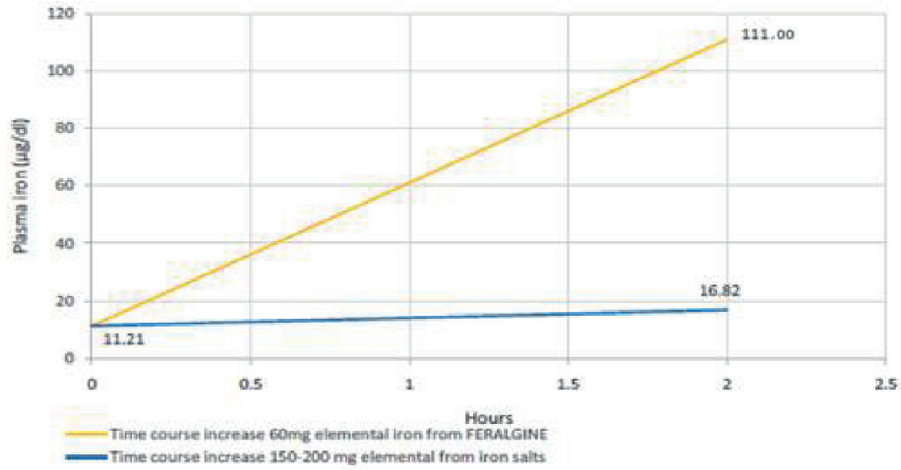

Figure 6.
Expected theoretical plasma iron level after 2 hours from 200 mg of elemental iron salts administration (blue lines) versus experimental FBC-A 60 mg elemental iron oral administration (yellow line) [34].

iron-deficient than adults (55%). The efficacy of oral iron treatment might be hampered by a significant incidence of gastrointestinal side effects and the exacerbation of an existing colitis, that limit adherence to therapy in near half of patients [35]. It has been shown that in adults the adherence to therapy lowers to 10–42% within 2 months. Consequently treatment with oral iron results in failure to control anemia in 2 out of 3 IBD patients as reported by Lugg et al. [36] According to the last European Crohn's and Colitis Organization [ECCO] guidelines, oral iron therapy is recommended for patients with mild IDA and clinically inactive IBD, with no history of intolerance to oral iron; instead intravenous (IV) administration iron should be considered in patients with clinically active IBD with previous intolerance to oral iron [37]. However although adverse reactions to modern IV iron formulations are rarely severe, given the potentially fatal side effects this treatment is generally only performed in a hospital setting where ready access to resuscitation equipments is available. Furthermore IV treatment has a significant incremental cost respect to oral iron treatment [37]. A recent review by Foteinogiannopoulou et al. on 1394 Greek patients with IBD showed that among those who received iron intravenously (393) about 89.3% responded, in contrast to only 54.2% of those who received iron orally (142). Furthermore 31% of patients that received iron orally presented with adverse events, mostly gastrointestinal symptoms that eventually led to cessation ofthe treatment. On the other hand, about 7.9% that received iron intravenously experienced adverse events during infusion. The availability of a well absorbed oral compound with good tolerability would be of great benefit for these patients, avoiding the need of intravenous treatment [38].

Vernero et al. performed a study with FBC-A in patients affected by IBD. They enrolled 52 patients with IBD, mean age 47 years (range 15–86 years) presenting with IDA. Mean Hb level was 11 g/dl (range 10.72–11.47 g/dl) and mean SF level was 21.4 ng/ml (range 3.09–39.7 ng/ml). Patients received FBC-A 30 mg once a day for 3 months. Response to therapy was monitored by periodical evaluation of Hb and SF. At the end of the study Hb mean value was 12.2 g/dl (range 11.6–12.52 g/dl) ($p = 0{,}0001$). Mean SF increased to 74 ng/ml (range 14.4–133.7 ng/ml), a difference near to the statistical significance ($p = 0{,}07$). Regarding FBC-Atolerability, 90% of patients reported good tolerance to treatment, while 10% of them experienced dyspepsia and worsening of diarrhea. Only 6% of patients suspended oral iron supplementation due to gastroenteric intolerance (adherence rate 94%) [39].

Sprecacenere et al. evaluated the impact of a 4 weeks course of FBC-A (30 mg/day) on a cohort of 52 blood donors presenting with IDA (mean Hb level11.8 ± 0.7 gr/dl and mean SF level 14.8 ± 9.8 ng/ml). After treatment mean Hb level increased to 13.3 ± 1 gr/dL (p = 0,007) and mean SF level to 21.8 ± 13.5 ng/ml (p = 0,02) [40].

Iron requirements drastically increase during pregnancy to accommodate an expandingred cell volume, growing fetus and placenta. The global prevalence of anemia in pregnancy is estimated to be approximately 38–42%. ID may be present in up to 80% of women in the second/third trimester of pregnancy and postpartum, if not supplemented with iron. Oral iron treatment is still considered a frontline therapy for IDA in pregnancy but gastrointestinal side effects are common leading to a high ratio of non-adherence to treatment [41]. Bertini et al. described 21 pregnant women with moderate IDA (Hb < 11 g/dl and SF < 25 ng/ml at time T0) supplemented with 30 mg/day of elemental iron in the form of FBC-A and evaluated at 15 days (T1) and 30 days (T2) of treatment. Hb and SF levels increased in all the enrolled women at T1 and T2 interval (Hb T1 *vs*. T0 $p < 0.004$; T2 *vs*.T0 $p < 0.00001$ and T2 vs. T1 $p < 0.003$) (SF T1 *vs*. T0 $p < 0.0001$; T2 *vs*. T0 $p < 0.00001$; T2 *vs.* T1 $p < 0.05$). This study provided evidence that a small quantity of elemental iron (30 mg/day in form of FBC-A) administered by oral route is rapidly effective in restoring Hb and SF levels in pregnant women affected by moderate IDA, without gastrointestinal adverse effects [42].

3. Discussion

It is well documented that ID/IDA impacts negatively on the affected patients by disturbing multiple organs function possibly leading to a multitude of symptoms that compromise the general well-being, quality of life and individual performance. Successful management of ID/IDA primarily requires identification and treatment of the underlying cause(s) of the ID. After that replacement should be established for all patients with IDA/IDA with or without symptoms. Oral iron salts such as ferrous fumarate, ferrous gluconate, and ferrous sulfate have been the mainstay of oral iron supplementation as they are inexpensive, effective at restoring ironbalance, and have a good overall safety and tolerability profile. However, in several patients absorption of oral iron salts is inadequate, and poor tolerance results in reduced adherence to therapy. Some other compounds are nowavailable as alternative therapies. Usually they have a more tolerability profile over the traditional iron salts but often no studies comparing the clinical or cost effectiveness of these different oral iron products are available.This short review summarizes all clinical studies on FBC-A published so far.

Several studies demonstrated that OIAT is a good index for the evaluation of iron absorption and might a reliable test to investigate the bioavailability of the various iron formulations [29–31]. The studies of Giancotti et al. [32], Talarico et al. [33] and Rondinelli et al. [34] performing OIAT clearly show as the FBC-A is well absorbed and well tolerated. Furthermore these studies evidence as the compound is useful to restore Hb and SF levels confirming as combination between FBC and AA adds a very safe profile in terms of gastrointestinal adverse events and taste, improving patient's compliance.

Most of patients with GI has impaired iron absorption and develop ID/IDA. They often do not tolerate FS or other ironcompounds, leading to forms of refractory IDA resistant to treatment. Our review clearly show as FBC-A may be effective in CD [32, 33] and IBD [39] that represent frequent causes of refractory IDA. Then this new oral iron formulation appears promising in terms of safety and efficacy for these patients and might be suggested as first-line treatment. So far there are not studies regarding the use of

FBC-A in other rare forms of impaired iron aborption as those found in gastrectomized patients or in patients with achloridria. Parenteral iron treatment is often recommended in these conditions. We believe that FBC-A might play a role in their management. However future studies are advisable.

Our previous study clearly showed that FBC is well absorbed in pediatric patients with CD [31]. Two other studies from our group reported in this review confirmed the good absorption and tolerability also for FBC-A in celiac patients with overt CD and during the first months of GFD [32, 33]. In our opinion these results support the possibility that this preparation might be considered the treatment of choice for celiac patients with ID/IDA. Despite these clinical results the mechanism underlying the good absorption of FBC-A in CD remains unclear. Many studies have shown that aminoacid-chelated iron is better absorbed and better tolerated than FS and other types of inorganic iron [9–12]. In particular it has been demonstrated that low dosage of FBCis equal or better than standard dosage of FS in adults, in infants and in children [43–45]. The intestinal absorption of non-heme iron is mediated by DMT1 that is less expressed in CD as a consequence of the mucosa's lesions. This situation may explain why non-heme iron is less absorbed in this disease. Recent studies in pigs showed how FBC increases transcription of DMT1 and PepT1 genes, this latter coding for a heme-iron transporter. Therefore, the author suggested that FBC might be absorbed also as heme-iron, via the PepT1 [46]. Other studies revealed as FBC is absorbed intact by intestinal cells, highlighting the possibility that FBC absorption may occur also independently of the presence of DMT1 [47]. Moreover, latest findings of a slow and constant release of iron from FBC-A might explain the high bioavailability of iron, also in CD patients [25].

When to use IV versus oral iron administration in patients with IBD still represents an on-going topic of debate between clinicians [48]. According to the last ECCO consensus paper the usual treatment of IDA per os has relevant limitations in IBD patients, in factoral iron formulations use is restricted due to poor tolerability and patient compliance. The same consensus paper underlines as IV iron is more effective, shows a faster response, and is better tolerated than oral iron [37]. However although new IV iron formulations have proved to be bettertolerated and lead to a faster Hb rise than oral iron, there is still hesitancy among gastroenterologists to promote this administration due to its risk of hypersensitivity reactions [38]. The results obtained by Vernero et al. on IBD patients highlight as FBC-A is effective and well tolerated in subjects with intestinal mucosa lesions who generally are poor responders to oral iron treatment and have reduced compliance. If these data will be confirmed on larger cohorts, FBC-A might be considered a good candidate for the first-line treatment in patients with IBD and ID/IDA, avoiding IV approach. It would be interesting to compare FBC-A treatment versus IV formulations in large comparative trials.

Milman et al. showed as FBC 25 mg iron is as effective as FS 50 mg iron in the prophylaxis of ID/IDA during pregnancy in a randomized trial [43]. The paper of Bertini et al. confirmed the benefit of FBC-A 30 mg/die in pregnancy. Considering the good absorption and the low side effects, FBC-A might be an useful alternative to FS in pregnant women who often display poor compliance to oral iron preparations.

Oral iron is often poorly tolerated in patients with iron deficiency secondary to infection, inflammation, renal and malignant diseases, or in elderly, particularly because of abdominal discomfort and poor absorption [1–4, 49, 50]. Considering the results obtained witha low FBC-A dose, it might be beneficial in these clinical scenarios.

Our review has some limitations, mainly related to the limited number of patients enrolled in each clinical trial and the heterogeneity of these patients. Finally no studies comparing the clinical or cost effectiveness of FCB-A to FS are available.

4. Conclusions

The major challenges in the management of ID/IDA are related to the tolerability and side effects of oral iron therapy. Therefore, it is crucial to tailor the most appropriate form, dosage and duration of treatment for each patient, in order to successfully replenish iron stores.

The data presented in this short review underline the efficacy and safety of the treatment with FBC-A, and support the use of this compound in patients with ID/IDA. This review provides also preliminary evidence to suggest FBC-A as first-line treatment of ID/IDA in patients with CD. For patients with IBD further clinical trials are warranted comparing FBC-A to IV iron replacement. Finally, as it is widely assumed that poor absorption and side effects limit iron treatment compliance in several other clinical conditions as during pregnancy and in elderly, this new iron formulation seems very promisingfor the treatment of ID/IDA in these settings.

Conflict of interest

Valentina Talarico, Laura Giancotti, Mazza Giuseppe Antonio, Roberto Miniero declare no conflict of interest. Marco Bertini is R&D in the Pharmaceutical Company Laboratori Baldacci SpA.

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