The role of ferric carboxymaltose in the treatment of iron deficiency anemia in patients with gastrointestinal disease

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***Abstract*:** Iron deficiency anemia (IDA) is the most common form of nutritional anemia worldwide. Iron plays a pivotal role in vital functioning of almost every organ system. IDA affects both physical and psychological functioning of humans. Oral iron is considered as first-line therapy for the treatment of IDA due to low cost, good safety profile and ease of administration. However, the absorption of oral iron is affected by several factors and incidence of gastrointestinal side effects can lead to lack of adherence to therapy as well as poor efficacy. This has led to the emergence of intravenous iron therapy which is clearly superior to oral iron with higher increment of hemoglobin levels and rapid replenishment of iron stores. Ferric carboxymaltose (FCM) is a novel non-dextran intravenous iron form which has been approved for use in patients with iron deficiency who have had inadequate response to oral iron therapy, intolerance to oral iron, or nondialysis-dependent chronic kidney disease. The safety and efficacy of using FCM for the treatment of IDA has been demonstrated in several clinical trials. One dose can provide a large amount of iron and has a very short infusion time. It should be considered as first-line therapy in patients with active inflammation like inflammatory bowel disease when gastrointestinal absorption of oral iron may be compromised. It should also be given to patients who have inadequate response to oral iron therapy. It has been shown to be noninferior to other intravenous iron formulations with a good safety profile and produced fewer anaphylactic reactions.

Keywords: anemia, iron deficiency, gastrointestinal diseases

Introduction

Iron deficiency (ID) is the most common cause of anemia, with the World Health Organization estimating it affects about 30% of the population worldwide [WHO, 2015]. The population in the United States has a more preferable prevalence of 2–5% (5% in individuals aged 2–15 years, 2% in those aged 16–69 years and 3% in those aged over 70 years) in men and 6–12% (12% in individuals aged 12–49 years, 9% in those aged 50–69 years and 6% in those aged over 70 years) in women [CDC, 2002]. ID is defined as decreased total iron content in the body. ID anemia (IDA) is defined as ID significant enough to affect erythropoiesis. The prevalence of ID without anemia was found to be even more common, occurring in about 11% of women and 4% of men in the United States [Looker *et al.* 1997]. Gastrointestinal (GI) disorders can contribute to ID, which prompts a need for better awareness of the subtleties of anemia as well as the importance of treating patients with IDA appropriately and effectively.

Physiology

In a state of homeostasis, about 1–2 mg of iron is absorbed and lost by the body every day. The duodenal enterocytes absorb a small portion of dietary iron per day (1–2 mg of an average of 18 mg consumed each day) [Andrews, 1999]. Diet contains iron in two forms: ferrous iron and ferric iron. The ferrous iron transporter located on the apical brush border of predominantly duodenal enterocytes facilitates the absorption of ferrous iron. Ferric iron is the most important iron in the

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diet but is converted to ferrous iron by iron reductase produced by brush border of the duodenal enterocyte. Iron circulates in the blood bound to transferrin and travels to the bone marrow where two-thirds of it is incorporated into hemoglobin in erythroid precursors and mature red blood cells (RBCs). Approximately 10–15% is utilized by the muscles in the form of myoglobin and other tissues. Iron is primarily stored in liver (1000 mg) and reticuloendothelial macrophages (600 mg) [Andrews, 1999]. Those macrophages serve usable iron by degrading hemoglobin in old red cells and reloading iron onto transferrin for delivery to tissues.

Role of hepcidin in iron metabolism

Iron homeostasis is tightly controlled by the absorption of iron in the duodenum which is regulated by hepcidin, an antimicrobially acting acute phase protein [Stein and Dignass, 2012]. Hepcidin levels are variable and depend on the level of iron in the body. The expression of the hepcidin gene (hepcidin antimicrobial peptide or HAMP) is found mainly in the liver but also to a smaller extent in macrophages, adipose tissue, small and large intestinal mucosa, muscles, heart and lungs [Atanasiu *et al.* 2007]. Hepcidin binds to a basolateral iron efflux transporter called ferroportin, which in turn binds to another protein, janus kinase 2 (JAK-2). Once ferroportin binds and activates JAK-2, it triggers phosphorylation of ferroportin [De Domenico *et al.* 2009]. The cell surface expression of ferroportin regulates the movement of intracellular iron into plasma. Thus hepcidin acts as a master regulator of iron absorption by modulating ferroportin. In a sense, with excess iron, hepcidin levels increase, which thereby decrease iron absorption by duodenocytes. However, hepcidin, as an acute phase reactant, can also increase in the setting of active inflammation, also reducing duodenocyte iron absorption perhaps at a time when the body requires more iron. Due to this, in a study of those taking oral iron replacement, hepcidin was found to be a better predictor of responsiveness to treatment than the severity of anemia [Bregman *et al.* 2013].

Signs and symptoms

Iron has a physiologic role in the functioning of almost every organ system. It is important for oxygen transport, mitochondrial functioning and synthesis, and degradation of proteins in the body. So ID not only compromises tissue oxygen delivery but also affects proliferation, differentiation, immune function and energy metabolism [Ghosh, 2006]. It also affects T-cell and macrophage function and reticulendothelial function. However, it is very important to note that ID in itself, in the early stages can contribute to many signs and symptoms in the absence of anemia. The symptoms also depend on the rapidity of onset of anemia and the degree of severity. ID can present with nonspecific symptoms like fatigue, weakness, exercise intolerance and poor concentration, which often go unnoticed. Patients realize these symptoms are related to ID only when they improve after treatment. Some patients with ID with or without anemia may have pica, glossitis, koilonychia and alopecia. It can diminish attention span, reduce school performance and affect growth in children [Pollitt, 2001]. Other symptoms like nausea, motility disorders, hypothermia, pallor of skin, exertional dyspnea, tachycardia, palpitations, risk of heart failure, cardiac hypertrophy and menstrual problems and loss of libido usually occur in later stages when anemia has set in with low hemoglobin. It can lead to reduced work capacity by affecting oxygen transport to tissues [Beard, 2001]. IDA also has a significant impact on physical function and mental health, documented by poor mental quality of life similar to those with depression, and poor physical quality of life similar to those who have myocardial infarction [Rapp *et al.* 1999; Evstatiev *et al.* 2011]. Thus, it is important to test for ID in patients who may present with more global, nonspecific symptoms, especially in the setting of chronic GI diseases.

Diagnosis

The World Health Organization defines anemia as hemoglobin less than 12 g/dl in nonpregnant women over 15 years and less than 13 g/dl in men over 15 years of age [WHO, 1998]. Initial workup includes complete blood count (CBC) with differential, serum ferritin, transferrin saturation, creatinine, C-reactive protein (CRP) and reticulocyte count [Gasche *et al.* 2007]. More extensive workup should be performed if initial evaluation cannot identify the cause of anemia. This includes serum concentrations of transferrin, vitamin B12, folic acid, haptoglobin and lactate dehydrogenase. If no etiology is identified after extensive workup, hematology referral may be needed for consideration of bone marrow etiology. The gold standard test for diagnosis of ID is bone marrow

aspirate which by definition is less than 10% of normoblasts staining blue with Prussian blue [Rimon *et al.* 2002]. This is not routinely performed in clinical practice as other simple, noninvasive tests are able to make the diagnosis.

The degree of ID can be predicted by serum ferritin and transferrin saturation, which can determine the adequacy of iron stores in the body. The criteria for diagnosis of IDA in patients without clinical or biochemical evidence of inflammation is ferritin less than 30 μg/liter or transferrin saturation less than 16%. But in the presence of inflammation, ferritin less than 100 μg/liter is considered diagnostic of IDA because ferritin acting as an acute phase reactant protein is elevated in inflammatory states [Bartels *et al.* 1978].

ID progresses in stages beginning with depletion of storage iron compartment (stage I), followed by diminished transport iron (stage II), and lastly, depletion of functional iron compartment (stage III) [Tussing-Humphreys *et al.* 2012]. In stage I of ID, the iron stores that comprise ferritin and hemosiderin laden macrophages in bone marrow, liver and spleen are depleted and the only laboratory evidence of this stage is low ferritin. Once iron stores are depleted, ID progresses to stage II, with depletion of transport iron and iron-deficient erythropoiesis. This is the stage of ID that is commonly seen in the United States [Cook *et al.* 1986]. Most patients do not have anemia even at this stage evidenced by normal hemoglobin and hematocrit, but by abnormal labs showing low ferritin, low serum iron, low transferrin saturation, high total iron binding capacity (TIBC) and increased soluble transferrin receptor. The last stage of ID (stage III) affects the functional iron compartment, comprising hemoglobin, myoglobin and cytochromes. The effect on hemoglobin synthesis leads to production of small RBCs (microcytic) and RBCs with low hemoglobin (hypochromic) and manifests with low hemoglobin along with all the other changes in lab indices.

Causes of IDA

The causes of IDA can be broadly classified into two categories: decreased iron absorption/intake and increased iron loss/use [Annibale *et al.* 2001; Bayraktar and Bayraktar, 2010]. The most common causes of IDA secondary to GI disorders are listed in Table 1. Loss of iron leading to IDA is seen with lesions causing bleeding, like peptic ulcer disease, angiodysplasia, inflammatory bowel disease (IBD), aspirin or nonsteroidal anti-inflammatory drug induced ulcers, GI neoplasias, diverticular bleeding, postoperative bleeding, and rarely from large hiatal hernias (Cameron lesions) and hook worm infestations [Annibale *et al.* 2001; Gasche *et al.* 2004; Goldberg, 2013].

IDA secondary to reduced absorption is either from reduced intake (nutrition) or from damage to enterocytes. Common causes of reduced absorption are chronic gastritis, celiac disease, IBD, intestinal lymphoma, intestinal bypass surgery, short gut syndrome, gastrectomy and gastrojejunostomy and bacterial overgrowth [Hershko and Patz, 2008; Ruz *et al.* 2009; Ott *et al.* 2012].

ID in patients with IBD: the role of hepcidin in inflammation

The prevalence of IDA in the IBD population is significantly higher than in the general population, affecting 72% of children, 42% of adolescents and 40% of adults [Goodhand *et al.* 2012]. The prevalence is even higher in hospitalized patients, with 74% affected compared with only 20% of outpatients with IBD [Gisbert and Gomollon, 2008]. IDA is associated with increased hospital visits and profoundly decreased quality of life [Gasche *et al.* 1997, 2007; Wells *et al.* 2006].

An important aspect in patients with IBD is the multifactorial etiology of IDA. Patients with IBD have increased blood loss from ulcerations and inflamed mucosa, reduced absorption due to damaged enterocytes, as well as an increase in hepcidin reducing oral absorption of iron.

As previously mentioned, with active inflammation, hepcidin binds to ferroportin (the key transporter of iron from the duodenocytes into the bloodstream) leading to its internalization and trapping of iron in the enterocytes and macrophages. This leads to functional hypoferremia [Dudkowiak *et al.* 2013]. Hepcidin, in theory, can be a useful marker to differentiate IDA from anemia of chronic disease (secondary to inflammation), as its level will be higher in anemia secondary to inflammation [Bergamaschi *et al.* 2013]. The level of hepcidin and its precursor, prohepcidin, was higher in patients with IBD, especially those with active disease compared with healthy controls, and had a positive correlation with other inflammatory markers like CRP, interleukin 6

Table 1. Oral iron formulations.

Formulation	Elemental iron	Dosage forms available	Additional information
Carbonyl iron	15–45 mg	Tablets, chewable tablets, suspension	Not an iron salt Slow release
Ferric ammonium citrate	25 mg	Capsules	Less bioavailable than ferrous salts
Ferrous bisglycinate	27 mg	Capsules, tablets	May be less likely to cause GI intolerance
Ferrous fumarate	50–150 mg	Tablets, chewable tablets	Similar efficacy/tolerability as ferrous sulfate Almost tasteless
Ferrous gluconate	27–38 mg	Tablets	Similar efficacy/tolerability as ferrous sulfate
Ferrous sulfate	65 mg	Oral solution, tablets, EC tablets, film-coated tablets	Common formulation
Heme-iron polypeptide	12 mg	Capsules	Animal origin
Polysaccharide–iron complex	150 mg	Capsules, solution, film-coated tablets	Promoted to cause less GI irritation (unproven)

GI, gastrointestinal; EC, enteric-coated.

and ferritin [Kaya *et al.* 2011; Oustamanolakis *et al.* 2011]. Thus, when deciding on treatment of ID in patients with IBD, the role of hepcidin and its potential to limit oral absorption of iron should be taken into account.

Treatment of IDA

The primary goal of treating IDA should involve diagnosing the underlying etiology of the anemia and treating this underlying disease. Otherwise, treating only the ID may lead to recurrence, especially if the underlying disease or disorder is chronic. However, while undergoing diagnostic evaluation or while the treatment of the underlying etiology is underway, patients can benefit from iron replacement to immediately help counteract their symptoms of IDA. Iron can be replaced either enterally or parenterally, with both methods having their own benefits and risks.

Enough iron should be administered to replete the iron deficit in the body. The Ganzoni formula can calculate the dose of iron required to restore hemoglobin levels: iron deficit (mg) = bodyweight (kg) × (target hemoglobin − actual hemoglobin) (g/dl) × 2.4 + iron storage depot (mg) [Ganzoni, 1970].

Oral iron replacement

Oral iron therapy is considered standard for patients with hemoglobin concentrations at least 10g/dl and CRP less than 5.0 mg/liter due to lower cost and ease of administration [Wc, 2008]. The Center for Disease Control recommends 30 mg/day of elemental iron intake to prevent development of IDA and about 60–120 mg/day for treatment. Delayed-release or enteric-coated iron formulations can bypass key absorption sites, so simpler formulations should be used whenever possible [McDiarmid and Johnson, 2002; Wc, 2008]. Although oral iron can be taken in divided doses, once daily dosing can improve compliance. The recommendation is to take oral iron before meals and along with vitamin C for better absorption [Wc, 2008].

There are two main forms of iron salt based on the chemical form of iron (ferrous *versus* ferric irons). There are several formulations (amino acid chelates, carbonyl iron and polysaccharide iron complex) and galenic forms (slow *versus* quick release) available on the market [Wc, 2008; Santiago, 2012]. However, in clinical practice ferrous salts are widely used: ferrous sulfate, ferrous gluconate and ferrous fumerate. Ferrous sulfate is the standard treatment of choice for IDA due to its general tolerability, effectiveness and low cost, with 20% elemental iron content. Ferrous fumerate and gluconate have similar efficacy and tolerability as ferrous sulfate with variable elemental iron content (ferrous fumerate 33% and ferrous gluconate 12%). A comparison of the different iron salts and formulations is presented in Table 1.

Ferric salts are available in the form of iron ferric ammonium citrate and polysaccharide iron complex. Ferric ammonium citrate is the most commonly used ferric salt, which requires conversion to ferrous form in the intestinal lumen. Polysaccharide iron complex is another ferric preparation which has ferric iron complexed with hydrolyzed starch with similar bioavailability as ferrous sulfate. Ferric salts are less commonly used as they have poor absorption, higher cost and a greater number of doses is needed to reach the desired level compared with ferrous salts [Santiago, 2012]. The bioavailability is also three times higher for ferrous salts compared with ferric preparations.

Other formulations are carbonyl iron, ferrous bisglycinate and heme-iron polypeptide. Carbonyl iron is a slow release preparation which contains micro particles of elemental iron with 100% elemental iron content and less toxicity than iron salts. Ferrous bisglycinate is an iron amino acid chelate with relatively higher bioavailability as the conjugation prevents formation of insoluble ferric hydroxide in the small intestine. This preparation is known to cause fewer GI side effects than ferrous salts. Heme-iron polypeptide is an animal-derived product which contains hemoglobin derived from porcine RBCs with more bioavailability and tolerance.

Patients notice a difference in overall wellbeing in the first few days of treatment. The first response seen on labs is reticulocytosis, which is seen with moderate to severe anemia in the first 7–10 days [Brugnara *et al.* 1997]. This is followed by a rise in hemoglobin which begins after 1–2 weeks of treatment and increases about 2 g/dl in the next 3 weeks. A rise in hemoglobin by 1 g/dl in the first month is considered an adequate response to treatment [Short and Domagalski, 2013]. The hemoglobin deficit is corrected by half in 1 month and returns to normal in 6–8 weeks. Oral iron should be continued for up to 3 months to replenish the body's iron stores [Goddard *et al.* 2011]. Serum ferritin is another useful marker which correlates to adherence to therapy and replenishment of iron stores. But ferritin starts to rise after the anemia is corrected. Another marker to predict response is serum transferrin receptor which changes with iron replacement [Thomas and Thomas, 2002]. Major predictors of response to oral iron therapy were studied by Bregman and colleagues. Significant predictors that were identified in this study are low hemoglobin, low hepcidin, high TIBC and low ferritin, but not iron level or transferrin saturation [Bregman *et al.* 2013].

Although patients can easily replace their ID by oral iron, there are some drawbacks to oral replacement. Oral iron needs to be monitored for response, tolerance and adherence [Gasche *et al.* 2007; Stein and Dignass, 2012]. A significant fraction of ingested iron remains unabsorbed. Concomitant medications and diet may limit oral iron absorption. Food in the stomach can decrease iron absorption by 40–50%. Medications that raise gastric pH (antacids, H_2 blockers, proton pump inhibitors) interfere with iron absorption [Goldberg, 2013]. Quinolone antibiotics should be avoided as they form complexes with iron, decreasing the efficacy of quinolones and preventing iron absorption [Kara *et al.* 1991; Goldberg, 2013]. Studies have shown that phytates from bran and tannates from tea also interfere with iron absorption [Disler *et al.* 1975; Hallberg *et al.* 1987; Goldberg, 2013].

Intolerance due to GI adverse effects results in discontinuation in up to 20% of patients [Lindgren *et al.* 2009]. The most common GI side effects are nausea, vomiting, abdominal pain, constipation and melena-like stools [Cancelo-Hidalgo *et al.* 2013]. The upper GI symptoms are more dose dependent and can be managed with less frequent and lower doses. However, lower GI side effects like constipation are not related to dosing. The sustained release forms have fewer upper GI side effects like nausea and abdominal pain, but discontinuation rates are similar to conventional formulations. Extended release formulations have improved compliance but decreased absorption due to release of iron past absorption sites in the duodenum and proximal jejunum. A systematic review done by Cancelo-Hodalgo and colleagues has shown the adherence to different oral iron formulations ranges between 40% and 60% [Cancelo-Hidalgo *et al.* 2013]. Therefore, if patients can tolerate oral iron, and do not have evidence of active inflammation, this is an inexpensive option for treating IDA.

Intravenous iron replacement

Intravenous iron is administered in the form of iron carbohydrate complexes [Geisser and Burckhardt, 2011]. It consists of a mineral core that is surrounded by a carbohydrate shell. The function of the carbohydrate shell is to stabilize the complex and reduce the risk of hypersensitivity

Table 2. Intravenous iron formulations.

Intravenous iron agent	FDA-approved indication
Iron dextran	Treatment of patients with iron deficiency when oral administration is unsatisfactory or impossible
Sodium ferric gluconate	Treatment of IDA in adult and pediatric patients (⩾6 years of age) with CKD receiving hemodialysis who are receiving supplemental epoetin therapy
Iron sucrose	Treatment of IDA in adult and pediatric patients at least 2 years of age with CKD
Ferumoxytol	Treatment of IDA in adult patients with CKD
Ferric carboxymaltose	Treatment of IDA in adult patients: who have intolerance to oral iron or have had unsatisfactory response to oral iron who have nondialysis-dependent CKD

Venofer (iron sucrose injection): full prescribing information from American Regent, Inc., Shirley, NY 11967, USA; 2000.
Dexferrum (iron dextran injection): full prescribing information from American Regent, Inc.; 2008.
Injectafer (ferric carboxymaltose injection): full prescribing information from American Regent, Inc.; 2013.
Feraheme (ferumoxytol injection): full prescribing information from AMAG Pharmaceuticals, Inc., Waltham, MA 02451, USA; 2015.
CKD, chronic kidney disease; FDA, US Food and Drug Administration; IDA, iron deficiency anemia.

reactions. When administered, complexes are taken up by reticuloendothelial macrophages. Various formulations of intravenous irons differ by the stability of the complex. All formulations approved for use in the United States by the Food and Drug Administration (FDA) are listed in Table 2.

The intravenous formulations of iron are more effective and correct anemia more rapidly than oral preparations as they circumvent the problem of iron absorption in the gut [Macdougall *et al.* 2014; Onken *et al.* 2014; Vadhan-Raj *et al.* 2014]. It also overcomes the problem of low adherence associated with oral therapy [Bayraktar and Bayraktar, 2010]. Intravenous iron administration bypasses the negative role of hepcidin's effect on duodenocytes when given parenterally. The main benefits of intravenous iron are quick absorption, larger doses of iron per treatment, and improved absorption in the setting of active inflammation.

A randomized controlled trial was performed by Lindgren and colleagues comparing the efficacy, safety and tolerance of oral iron *versus* intravenous iron in the form of iron sucrose [Lindgren *et al.* 2009]. A total of 91 patients with IBD and IDA were randomized to receive intravenous iron sucrose *versus* oral iron and were followed for a total of 20 weeks. The patients reached their reference levels more in the intravenous iron group (oral iron 22% *versus* intravenous iron 42%) and fewer patients had anemia after intravenous treatment (oral iron 41% *versus* intravenous iron 16%). Intravenous iron replacement was shown to be effective, safe, well tolerated and superior to oral iron in correcting hemoglobin and iron stores in this cohort of patients with IBD.

Ferric carboxymaltose

Ferric carboxymaltose (FCM) is a novel dextran-free intravenous iron which consists of a ferric hydroxide core stabilized by a carbohydrate shell [Lyseng-Williamson and Keating, 2009]. This allows controlled delivery of iron to the cells of the reticuloendothelial system and subsequent delivery of iron-binding proteins. FCM is effective in the treatment of IDA by delivering a large dose of iron during a minimum administration time. It can provide up to 1500 mg of iron in just two administrations of 750 mg given at least a week apart. FCM can be administered as an intravenous infusion over 15 min or a slow push over at least 7.5 min. It does not require a test dose but patients need monitoring for signs and symptoms of hypersensitivity during and after administration for at least 30 min. FCM is shown to be noninferior with similar or superior efficacy compared with oral iron and other intravenous iron preparations. The safety profile has also been evaluated in several clinical trials performed for different indications.

A study comparing FCM with oral iron sulfate in terms of safety and noninferiority followed patients with IDA secondary to IBD for 12 weeks

[Kulnigg *et al.* 2008]. The median rise in hemoglobin was comparable in both groups. The response (defined as a rise in hemoglobin >2 g/dl) was higher in the intravenous iron group in the first 4 weeks, proving that the correction is faster with intravenous iron. In addition, oral iron was discontinued more often due to adverse events (iron sulfate 7.9% *versus* FCM 1.5%). FCM also sufficiently refilled iron stores as noted by a median increase in ferritin.

Onken and colleagues compared the efficacy and safety of FCM in patients with IDA, with oral iron in one cohort (cohort 1; $n = 507$) and other forms of intravenous iron in the other cohort, the most common being intravenous sucrose (cohort 2; $n = 504$). The study included patients with IDA secondary to heavy uterine bleeding ($n = 250$), GI disorders ($n = 53$), postpartum hemorrhage ($n = 13$), dietary deficiency ($n = 24$) and other causes ($n = 159$) in cohort 1. Cohort 2 also had patients with IDA secondary to heavy uterine bleeding ($n = 220$), GI disorders ($n = 115$), postpartum hemorrhage ($n = 77$), dietary deficiency ($n = 6$) and other less common causes ($n = 80$). The mean increase in hemoglobin from baseline to day 35 was significantly greater in the FCM group than in the oral iron group (1.57 *versus* 0.80 g/dl; $p = 0.001$), regardless of etiology of IDA. *Post hoc* analysis revealed higher increases in hemoglobin in patients who took FCM compared with other intravenous iron formulations (2.90 *versus* 2.16 g/dl; $p = 0.001$). No differences in safety or adverse events were found between the FCM *versus* the other iron replacement groups: the proportion of patients reporting adverse events, potential clinically significant laboratory values and other components like all-cause mortality, congestive heart failure, arrhythmias, significant blood pressure variations or nonfatal myocardial infarction or stroke was 3.4% in the FCM group *versus* 3.2% in other comparison groups.

A randomized controlled multicenter trial comparing the efficacy and safety of FCM with iron sucrose in patients with IBD and IDA [Evstatiev *et al.* 2011] found that more patients receiving FCM had a better response, with a hemoglobin rise of at least 2 g/dl in 65.8% of the FCM group *versus* 53.6% of the iron sucrose group ($p = 0.004$). The drug-related adverse events were comparable between the two groups. Thus FCM was shown to be a better intravenous iron formulation with greater efficacy and good safety profile in this study.

Another open-label, randomized multicenter trial compared the efficacy and safety of FCM with iron dextran (DEX) in a total of 160 patients with IDA. Subjects randomized to the FCM group included patients with IDA secondary to heavy uterine bleeding ($n = 32$), chronic kidney disease ($n = 4$), IBD or GI disorders ($n = 31$), postpartum hemorrhage ($n = 2$), other causes ($n = 4$) and unknown causes ($n = 9$). Among the other group, there were patients with IDA secondary to heavy uterine bleeding ($n = 27$), chronic kidney disease ($n = 22$), IBD or GI disorders ($n = 30$), postpartum hemorrhage ($n = 1$), other causes ($n = 9$) and unknown causes ($n = 9$).The study showed comparable efficacy between the two groups (2.8 g/dl increase of hemoglobin in the FCM group *versus* 2.4 g/dl in the DEX group) [Hussain *et al.* 2013]. The adverse events were reported to be fewer in the FCM groups, with immune system disorders (0% in the FCM group *versus* 10.3% in the DEX group; $p = 0.003$) and skin disorders (7.3% in the FCM group *versus* 24.4% in the DEX group; $p = 0.004$). Five patients experienced severe adverse events (defined As death, life-threatening event, hospitalization, disability or congenital defects) in the FCM group compared with three patients in the DEX group. However, none of the adverse events were study drug related in the FCM group. Transient asymptomatic hypophosphatemia was observed in the FCM group (8.5% in the FCM group *versus* 0% in the DEX group). The efficacy and safety of FCM was retrospectively analyzed by Beigel and colleagues in 250 patients with IBD [Beigel *et al.* 2012]. In the treatment cohort, 83.1% of the patients had serum iron less than 60 μg/dl, 90.4% had ferritin up to 100 ng/ml and 66.7% had anemia. After treatment, 74.7% reached an iron concentration greater than 60 μg/dl, 61.6% had ferritin greater than 100 ng/ml and improvement of anemia was found in 90.7% of patients. The most frequently reported adverse event was transient increase in liver enzymes.

Evstatiev and colleagues performed another multicenter trial to evaluate the time to recurrence of anemia in patients with IBD within an 8-month study period [Evstatiev *et al.* 2013]. Anemia recurred in 26.7% of subjects given FCM and in 39.4% given placebo. The time to anemia recurrence was longer in the FCM group (hazard ratio 0.62; 95% confidence interval 0.38–1.00; $p = 0.049$). Adverse events including serious adverse events were comparable between the two groups. So the authors concluded that FCM

compared with placebo prevented recurrence of anemia in patients with IBD.

Adverse reactions

The most common adverse reactions (⩾2%) associated with FCM are nausea, hypertension, flushing, hypophosphatemia and dizziness. The proportion of serious anaphylactic reactions reported with FCM in clinical trials was 0.1%. The pathophysiology of these reactions is largely unknown but is thought to be secondary to release of free iron [Bircher and Auerbach, 2014; Rampton *et al.* 2014]. The incidence of hypersensitivity reactions and life-threatening complications is much lower with new iron formulations such as FCM; however, patients still need to be monitored for any infusion-related reactions [Auerbach and Ballard, 2010; Bayraktar and Bayraktar, 2010, Auerbach *et al.* 2013]. Other allergic manifestations like rash, itching, urticaria, wheezing and hypotension have been reported in about 1.5% of patients. Other drawbacks of intravenous iron therapy include the need for additional healthcare personnel or an infusion center for intravenous iron access and treatment, as well as higher cost. However, as a more efficacious and faster treatment option, cost effectiveness may equal or overtake oral replacement therapy, especially in a set cohort of patients.

Conclusion

IDA can contribute to many signs and symptoms, including poor physical and mental quality of life. Therefore, diagnosing ID is important as these symptoms can occur even in the early stages of deficiency before anemia sets in. Early treatment can improve signs and symptoms while the underlying etiology of IDA is being diagnosed and treated to prevent future recurrence. Although oral iron supplementation can be an inexpensive option to treat mild anemia and for those who can tolerate potential GI side effects, intravenous iron may be an appropriate first-line therapy in many patients with GI disease, including those with IBD and those with a hemoglobin level less than 10 g/dl. FCM offers a treatment option with the most amount of iron found in a single intravenous formulation, with a capability of more rapid and complete repletion of iron stores, and low side-effect profile.

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