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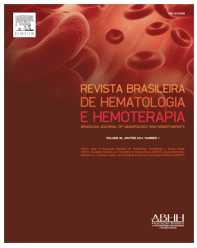

Review article

Intravenous ferric carboxymaltose for the treatment of iron deficiency anemia

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ABSTRACT

Nutritional iron deficiency anemia is the most common deficiency disorder, affecting more than two billion people worldwide. Oral iron supplementation is usually the first choice for the treatment of iron deficiency anemia, but in many conditions, oral iron is less than ideal mainly because of gastrointestinal adverse events and the long course needed to treat the disease and replenish body iron stores. Intravenous iron compounds consist of an iron oxyhydroxide core, which is surrounded by a carbohydrate shell made of polymers such as dextran, sucrose or gluconate. The first iron product for intravenous use was the high molecular weight iron dextran. However, dextran-containing intravenous iron preparations are associated with an elevated risk of anaphylactic reactions, which made physicians reluctant to use intravenous iron for the treatment of iron deficiency anemia over many years. Intravenous ferric carboxymaltose is a stable complex with the advantage of being non-dextran-containing and a very low immunogenic potential and therefore not predisposed to anaphylactic reactions. Its properties permit the administration of large doses (15 mg/kg; maximum of 1000 mg/infusion) in a single and rapid session (15-minute infusion) without the requirement of a test dose. The purpose of this review is to discuss some pertinent issues in relation to the history, pharmacology, administration, efficacy, and safety profile of ferric carboxymaltose in the treatment of patients with iron deficiency anemia.

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Introduction

Anemia is common. Nutritional iron deficiency anemia (IDA) is recognized as the most common nutritional deficiency disorder in both the developed and developing world, affecting more than two billion people. A 2008 World Health Organization (WHO) report, concentrating on pre-school children and women, estimated that worldwide one in four people were affected by IDA, with pregnant women and preschool-age

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Table 1 – Disadvantages of oral iron therapy.

Gastrointestinal adverse events
Lack of adherence to therapy
Insufficient length of therapy
Limited duodenal absorption due to concomitant gastrointestinal pathology (inflammatory bowel disease or any other cause of chronic inflammation, malignancy)
Long course therapy – 1 to 2 months to resolve anemia and 3 to 6 months to replenish body iron stores

children at the greatest risk.[1] High prevalences of anemia are associated with older age,[2] and with acute and chronic conditions, such as chronic kidney disease.[3]

In a population-based study designed to detect the prevalence of anemia in a healthy population of children (18 months to 7 years) and women (14–30 years) tested in 2006–2007 in the state of Rio Grande do Sul, Brazil, the median prevalence of anemia was 45.4% in 2198 children and 36.4% in 1999 women.[4] The high prevalence of IDA has substantial consequences not only on health but also on subsequent socioeconomic issues, including decreased work capacity and productivity.[1]

Oral iron therapy

Iron has been used to treat anemia for more than 300 years. However, it was not until the 19th century when Pierre Blaud introduced ferrous sulfate that iron therapy became the standard treatment for IDA.[4]

Treatment with oral iron supplements is simple, inexpensive and a relatively effective way of treating iron deficient conditions. If response does not occur within 3–4 weeks of suitable treatment, there is no reason to continue oral iron therapy. Rather, an explanation for failure should be sought. On the other hand, it is very well known that oral iron is a less than ideal treatment. Table 1 shows the main disadvantages of this therapy.

Noncompliance with a prescribed course of oral iron is common, and even in compliant patients, limited intestinal absorption fails to compensate for the iron needs in the presence of ongoing blood losses or inflammatory conditions.[5–7]

In addition, adequate iron stores are essential to achieve maximum benefit from erythropoiesis-stimulating agents (ESAs). Low iron stores and decreased availability of iron are the most common reasons for resistance to the effect of these agents. Thus, oral iron therapy should not be considered for chronic kidney disease (CKD) patients on hemodialysis and cancer patients receiving ESAs because of the inflammatory state. In this scenario, oral iron is poorly absorbed from the intestinal tract due to the upregulation of hepcidin, a peptide hormone that plays a central role in iron homeostasis.[8] In addition, in inflammatory bowel disease (IBD), the possibility that iron may further damage the intestinal mucosa should prompt serious thought about the use of intravenous (IV) rather than oral iron therapy.[9–14]

Intravenous iron therapy

Treatment with IV iron in some clinical situations could present some advantages over oral iron, such as faster and higher increases of hemoglobin (Hb) levels and body iron stores.[15–23]

Table 2 – Clinical indications for intravenous iron therapy.

Post-gastrectomy/bariatric surgery
Anemia of chronic kidney disease
Intestinal malabsorption syndromes
Anemia associated to inflammatory diseases
Inflammatory bowel diseases
Anemia of cancer
Intolerance to oral iron or non-compliance to an oral regimen
Iron-refractory iron deficiency anemias
Hereditary hemorrhagic telangiectasias (Osler-Weber-Rendu disease) and angiodysplasia due to other causes (in cases when oral iron is not tolerated or insufficient for treatment)

For these reasons, modern formulations of IV iron have emerged as a safe and effective alternative for IDA management.[9–14] The main clinical indications for IV iron treatment are listed in Table 2.

Newer intravenous iron formulations

In the last two years, three new IV iron compounds have been released for clinical use in patients with IDA. Two are currently approved for use in Europe (ferric carboxymaltose [FCM],[24–29] and iron isomaltoside 1000 [Monofer®][30] and one in the United States (Ferumoxytol [FeraHeme®]).[31–33]

In their pre-registration trials, all of these three new compounds could potentially have a better safety profile than the more traditional IV preparations, particularly because these products can be given more rapidly and in larger doses than their predecessors. They are promising for the complete replacement of iron within 15–60 min. The use of FCM in Brazil was recently approved by the Brazilian Health Regulatory Agency, *Agência Nacional de Vigilância Sanitária* (ANVISA).

Ferric carboxymaltose

FCM is a parenteral iron dextran-free product and the first of the new agents approved for rapid and high-dose replenishment of depleted iron stores.[24] FCM is an iron complex that consists of a ferric hydroxide core stabilized by a carbohydrate shell. The design of the macromolecular ferric hydroxide carbohydrate complex allows controlled delivery of iron to the cells of the reticuloendothelial system and subsequent delivery to the iron-binding proteins, ferritin and transferrin, with minimal risk of large amounts of ionic iron being released into the serum.[24]

FCM is a stable complex with the advantage of being non-dextran-containing and having a very low immunogenic potential and therefore not predisposed to high risk of anaphylactic reactions. Its properties permit the administration of large doses (15 mg/kg; maximum of 1000 mg/infusion) in a single and rapid session (15-minute infusion) without the requirement of a test dose.[25–28]

Efficacy of ferric carboxymaltose

The therapeutic efficacy of IV FCM has been evaluated in several randomized, Phase III, open-label, controlled, multicenter trials in a diverse range of conditions associated with absolute or functional iron deficiency with or without anemia. These conditions include patients with IBD, abnormal uterine bleeding (AUB), postpartum IDA, chronic heart failure (CHF), anemia in pregnancy in the second and third trimester, post-partum anemia (PPA) and CKD patients on hemodialysis or not. Most of these trials used oral iron as a comparator, and FCM was shown to have better efficacy compared to oral iron in terms of improvement of Hb levels particularly with regard to body iron replenishment (significantly faster and greater with FCM than ferrous sulfate).[3,24–28,34]

In most of these trials, patients received either FCM doses of ≤1000 mg, administered IV over ≤15 min or oral ferrous sulfate (FeSulf), 325 mg (65 mg iron) three times daily, or 304 mg (100 mg iron) twice daily.[3,24–28,34]

FCM was usually administered until the patient's calculated total iron replacement dose was achieved. Treatment with FCM improved indices of anemia: Hb, ferritin and transferrin saturation [TSAT] values.[34]

In patients on hemodialysis (HD) with IDA secondary to CKD, FCM demonstrated an efficacy comparable to iron sucrose (IS) in achieving an increase in Hb.[34,35]

In patients with IBD or PPA, improvements in Hb levels were more rapid with FCM than with FeSulf.[25,34,36]

Patients with PPA receiving FCM, compared to those receiving oral iron, achieved a ≥2.0 g/dL increase in Hb earlier (seven days versus 14 days; p-value <0.001) and were more likely to achieve a ≥3.0 g/dL increase in Hb at any time beginning on Day 14 (86.3% versus 60.4%; p-value <0.001). Moreover they were more likely to achieve an Hb level >12.0 g/dL by the end of the study (Day 42; 90.5% versus 68.6%, p-value <0.01). Serum ferritin increased in the IV FCM treatment group, but not in the oral iron group. Differences between groups were significant at each study time point. TSAT increased significantly at every time point in both groups; however, FCM-treated patients showed higher TSAT at each time point after the first week.[34,36]

FCM improved the quality of life of patients to an extent equivalent to oral FeSulf in patients with IBD or PPA, and to a greater extent than oral FeSulf in women with AUB.[25,27,34,36]

FCM also improved the quality of life as well as functional symptoms and exercise capacity in patients with CHF.[26,34]

A multicenter comparative study that compared the efficacy of FCM versus IS for correcting preoperative anemia in patients undergoing major elective surgery showed limitations of IS to achieve high-level iron repletion including the number and frequency of doses (maximum dose 500 mg per week) and duration of administration (60 min for a 200 mg dose). In contrast, FCM attained iron replenishment more frequently (82% versus 62%, respectively; p-value = 0.007) with fewer treatment sessions [2 versus 5, respectively; p-value = 0.001], showed a higher final Hb level with a trend toward a higher rate of anemia correction, and patients received intraoperative and/or postoperative blood transfusions less frequently. There were no IV iron-related life-threatening adverse events, and the frequency of mild adverse events was similar with both IV products.[37]

Ferric carboxymaltose safety

The safety of FCM was tested in a total of 20 phase II/III database trials that evaluated 5799 subjects exposed to FCM, a larger database than for any other IV iron formulation reported to date.[38]

In this larger database the event rates are compared between subjects exposed to FCM and subjects exposed to oral iron, any IV iron, or pooled comparators (including any IV iron formulation available at the time the trials were conducted, i.e. IS, ferric gluconate, or low and high molecular weight iron dextran, or oral iron as well as a placebo).[38] When comparing FCM to other IV iron formulations, the rates of nausea, injection site reactions (i.e. discoloration, extravasation, or pain), headache, hypertension, dizziness, constipation, vomiting and diarrhea are similar. The rates of dysgeusia and hypotension are lower in the FCM group compared with the other IV iron group. However, the rates of decreased blood phosphate, flushing, and increased alanine aminotransferase are higher in the FCM group than the other IV iron group. Drug-related adverse reactions reported by at least 1% of treated patients are shown in Table 3.[36]

Injection site reactions (i.e. discoloration, extravasation, pain) may occur with any IV iron formulations.[38] Such reactions were reported in 1.6% of subjects receiving FCM in the pooled phase II/III database compared with 1.8% of subjects receiving any other IV iron (Table 3).[38] These discolored regions may be long lasting (several months) and can be a cosmetic concern. It has been found that the incidence of injection site discoloration after FCM administration may be greatly reduced by the practice of flushing the infusion catheter with saline before withdrawing the needle to avoid dribbling of FCM into the subcutaneous tissue.[38]

Hypersensitivity reactions, including some that are fatal, are adverse events that occur to some extent for all IV iron formulations. So far, a single case of fatality has been associated with FCM.[39] Standard warning text is required by the FDA to be included in all the prescribing information of all IV irons marketed in the USA, advising that patients may present with shock, clinically significant hypotension, loss of consciousness, or collapse. The text states that it is necessary to monitor patients for signs and symptoms of hypersensitivity during and after IV iron administration for at least 30 min and until clinically stable following completion of the infusion. In addition, it is stated that such agents are administered only when personnel and therapies are immediately available for the treatment of serious hypersensitivity reactions. Similarly, the European Medicines Agency recently completed a review of post-marketing safety data for IV irons (including FCM) and concluded that all IV irons have a small risk of causing allergic reactions which can be life threatening if not treated promptly.[40] In the two primary FCM 750 mg trials, serious anaphylactic/anaphylactoid reactions were reported in 0.1% (2/1775) of subjects receiving FCM and 0.1% (1/1783) of subjects receiving a comparator.[38,39]

Table 3 – Drug-related treatment-emergent adverse events (%) (≥1% in the ferric carboxymaltose (FCM) group phase II/III database).[38]

	FCM ($n=5799$) (%)	Pooled comparators ($n=5272$) (%)	Oral iron ($n=2497$) (%)	Any intravenous iron ($n=2439$) (%)	p-Value[d]
Nausea	3.1	2.8	2.5	2.2	0.112
Decreased blood phosphorus	1.9[a]	2[a]	0[b]	0[b]	<0.001
Injection site reaction	1.6[a]	0.7[b]	0[c]	1.8[a]	<0.001
Headache	1.4	1.1	1.1	1.3	0.453
Hypertension	1.3[a]	0.7[b]	0.1[c]	1.4[a]	<0.001
Dizziness	1.2[a]	0.8[a]	0.3[b]	1.3[a]	<0.001
Flushing	1.0[a]	0.1[b,c]	0[b]	0.2[c]	<0.001
Increased alanine aminotransferase	1.0[a]	0.5[b,c]	0.8[a,c]	0.2[b]	<0.001
Dysgeusia	0.9[a]	1.0[a]	0.2[b]	2.0[c]	<0.001
Constipation	0.8[a]	4.1[b]	8.0[c]	0.4[a]	<0.001
Vomiting	0.7	0.9	1.0	0.8	0.532
Diarrhea	0.5[a]	1.1[b,c]	1.6[b]	0.7[a,c]	<0.001
Hypotension	0.5[a]	0.8[a]	0[b]	1.7[c]	<0.001

[a,b,c] Different letters represent statistical differences (p-value <0.05).

[d] Chi-square test.

Most of the hypertensive events in the FCM group occurred during the observation period immediately following study drug administration and most of them were resolved within 30 min. The FCM prescribing information recommends monitoring patients for signs and symptoms of hypertension following each FCM administration.[38]

A transient drop in blood phosphate was a finding in the clinical trials of FCM. None of the cases of hypophosphatemia in these trials was associated with serious adverse events. In nearly all cases there was no clinical sign except for the low laboratory value.[36,38,39,41,42] Hypophosphatemia is related to an increase in fibroblast growth factor 23 (FGF23) activity, an osteocyte-derived hormone that regulates phosphate and vitamin D homeostasis. Elevated FGF23 activity increased urinary excretion of phosphate, decreased calcitriol levels, and increased parathyroid hormone levels, causing (in some patients treated with FCM) transient, mostly asymptomatic hypophosphatemia.[38,42]

Regarding tolerability and the safety profile, the clinical trials with FCM evaluated 5799 subjects exposed to FCM and most drug-related adverse events were considered transient and mild to moderate in intensity. Treatment was not permanently discontinued in any patient due to adverse events. These studies concluded that FCM is well tolerated and with a clinically manageable safety profile when appropriate dosing, correct schedule of infusion and monitoring are used.[3,24–28,34]

No safety concerns have been identified in breastfed infants of mothers receiving FCM and administration in the second and third trimester of pregnancy is safe and effective.[43]

Conclusions

Oral iron supplements are an inexpensive and effective way of treating IDA patients and their administration, in the absence of inflammation or significant ongoing blood loss, can correct anemia, provided significant doses of iron can be tolerated.

In some clinical situations, oral iron is a less than ideal treatment because of the increased rate of gastrointestinal adverse events, particularly when using ferrous iron compounds, and the long course needed to resolve anemia and to achieve replenishment of body iron stores.

In cases where oral iron is ineffective, associated with adverse events or cannot be used, IV iron compounds are treatment options.

FCM has been available in Europe since its approval in 2007 and in the USA since 2009; it is currently marketed in over 50 countries and recently became available in Brazil.

Since 2007 several trials have been completed, confirming the safety and effectiveness of FCM in the treatment of IDA in a variety of clinical settings.

FCM permits a much higher single dose of IV iron to be administered over a shorter period.

Another indication for FCM is anemia associated to chronic inflammation, when elevated levels of hepcidin may induce proteolytic degradation of ferroportin molecules that are necessary for transporting iron from the gastrointestinal tract to the circulation.

The ability to treat IDA that is unresponsive to oral iron in a broad range of patients in one or two rapid administrations is likely to increase patients' compliance and may improve the quality of life and significantly reduce healthcare costs.

FCM represents an important new therapeutic modality that offers significant clinical benefit, and thereby can reduce morbidity and mortality from many pathological conditions associated with iron deficiency.

Overall, FCM is considered a new optimal treatment for parenteral iron administration, providing a very efficient and convenient means of delivering iron in patients with IDA.

Conflicts of interest

The authors declare no conflicts of interest.

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