

Ferric carboxymaltose: a breakthrough treatment for iron deficiency anaemia

Introduction

Iron is an essential element that is crucial to all major metabolic pathways. Among others, it plays a central role in the proteins that transport oxygen in the blood and muscles, i.e. haemoglobin and myoglobin, respectively. The metabolism of iron is highly regulated with efficient recycling of iron but no active excretion of iron. Homeostasis is typically maintained at the level of intestinal absorption; however, iron deficiency may arise from blood loss, impaired uptake, dietary deficiency and developmental demands such as pregnancy [1]. Iron deficiency is one of the most common nutrient deficiencies affecting an estimated two billion people worldwide (WHO health report 2002). If untreated, iron deficiency may lead to iron deficiency anaemia, whereas anaemia affects almost 25% of the world's population [2]. Iron deficiency anaemia has been linked to impaired physical and mental development, fatigue, weakened immunity, poor work performance and a decreased quality of life [3-5].

Therapeutic options for iron deficiency

Oral iron

Treatment ultimately involves identifying the underlying cause of the iron deficiency and replenishing the iron stores. Currently, oral supplementation is the first-line treatment though a significant number of patients do not tolerate or do not respond to oral iron therapy [6, 7]. In some studies, as many as 40% of patients reported side effects secondary to oral iron intake. Reported side effects usually occur within an hour after ingestion and include nausea, epigastric pain, vomiting, diarrhoea or constipation. Further limitations of oral iron treatment are impaired absorption, prolonged iron store repletion times and, particularly with concomitant erythropoiesis-stimulating agent (ESA) treatment, increased iron demands that cannot be matched by oral

iron supplementation [1, 8]. Accordingly, a significant number of patients discontinue oral therapy despite substantial iron deficiency and require IV iron as an alternative approach. Intravenous iron therapy is suitable in the following clinical situations [1]:

- intolerance to oral iron preparations
- severe iron deficiency where a rapid therapeutic effect is needed
- functional iron deficiency where the iron demand for haemoglobin synthesis exceeds the amount that can be mobilised from filled iron stores, e.g. in anaemia of inflammation or while using ESAs
- iron deficiency, where oral iron therapy is insufficient because of chronic blood loss
- malabsorption of iron due to intestinal disorders
- poor compliance to oral iron treatment
- risk of drug-drug interactions between oral iron and concomitant medication.

IV iron

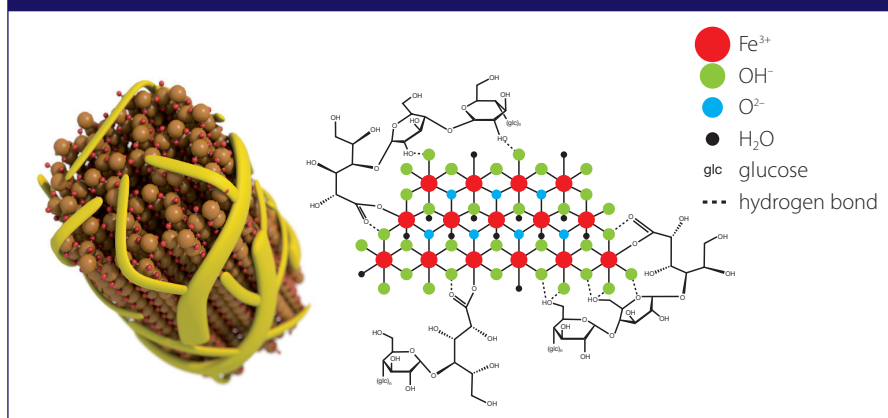
Until recently, the most commonly used IV iron preparations comprised iron dextran, iron gluconate, and iron sucrose. Although effective in replenishing iron

stores, each of these formulations has distinct limitations. Iron dextran is associated with reactivity to anti-dextran antibodies that can induce hypersensitivity reactions and anaphylactic shock [9, 10]. On the other hand, less robust iron complexes such as iron gluconate and to a lower extent iron sucrose release larger amounts of iron into the plasma [9, 10]. This can cause oxidative stress and loss of administered iron via renal excretion rather than incorporation into iron-binding proteins for utilisation in erythropoiesis. In an attempt to overcome these limitations, ferric carboxymaltose has been developed as a novel IV iron repletion therapy [1].

Ferric carboxymaltose

Ferric carboxymaltose represents a new generation of parenteral iron preparations that is currently approved in 17 EU countries (Austria, Czech Republic, Denmark, Estonia, Finland, Germany, Greece, Ireland, Latvia, Lithuania, The Netherlands, Poland, Portugal, Slovak Republic, Spain, Sweden and UK) as well as in Liechtenstein and Switzerland. During development the aim was to create a product that addresses the

Figure 1: Structure of ferric carboxymaltose [11]



Geisser P. The pharmacology and safety profile of ferric carboxymaltose Ferinject®: structure/reactivity relationships of iron preparations. *Port J Nephrol Hypert.* 2009;23(1):11-6. Printed with permission.

limitations of currently available IV iron products. In particular, the goal was to develop a formulation with the following properties:

- dextran-free and thus not reactive with anti-dextran antibodies
- safe to be administered in a high dose
- administered over a shorter time than current products
- heat sterilisable
- pH-neutral and nearly isotonic.

Ferric carboxymaltose is a dextran-free iron complex consisting of a polynuclear iron(III)-oxo-hydroxide core stabilised with a carbohydrate shell (see Figure 1). The core of ferric carboxymaltose resembles that of ferritin, the main intracellular iron storage protein. Ferric carboxymaltose is taken up in the reticuloendothelial system of the liver, spleen, and bone marrow [12]. The complex is degraded and the iron is made available for utilisation, i.e. incorporation in haemoglobin, or storage, i.e. incorporation in ferritin [1, 12]. As only very small amounts of unbound, labile iron are released into the circulation, the toxic effects of labile iron are avoided.

Administration of ferric carboxymaltose

Ferric carboxymaltose is supplied as a colloidal solution containing 5% iron in a single-use vial to be administered by

IV bolus injection or by drip infusion. Up to a maximal single dose of 1,000 mg iron per week can be administered by IV infusion within at least 15 minutes. Alternatively, up to a maximal single dose of 200 mg iron per day can be administered by IV injection maximally three times a week. The individual dose should not exceed 15 mg iron per kilogram of body weight [10]. The total therapeutic dose should be calculated from the degree of anaemia using the Ganzoni formula [13]:

$$\text{Total iron deficit (mg)} = \text{Body weight (kg)} \times (\text{Target Hb} - \text{Actual Hb}) (\text{g/L}) \times 0.24 + \text{storage iron (mg)}$$

This formula determines the body iron deficit by taking into account the haemoglobin deficit and the amount required to replenish the iron stores. As with all IV iron protocols, potentially life-threatening anaphylactoid reaction can occur with ferric carboxymaltose and life-saving equipment should be available.

Tolerability

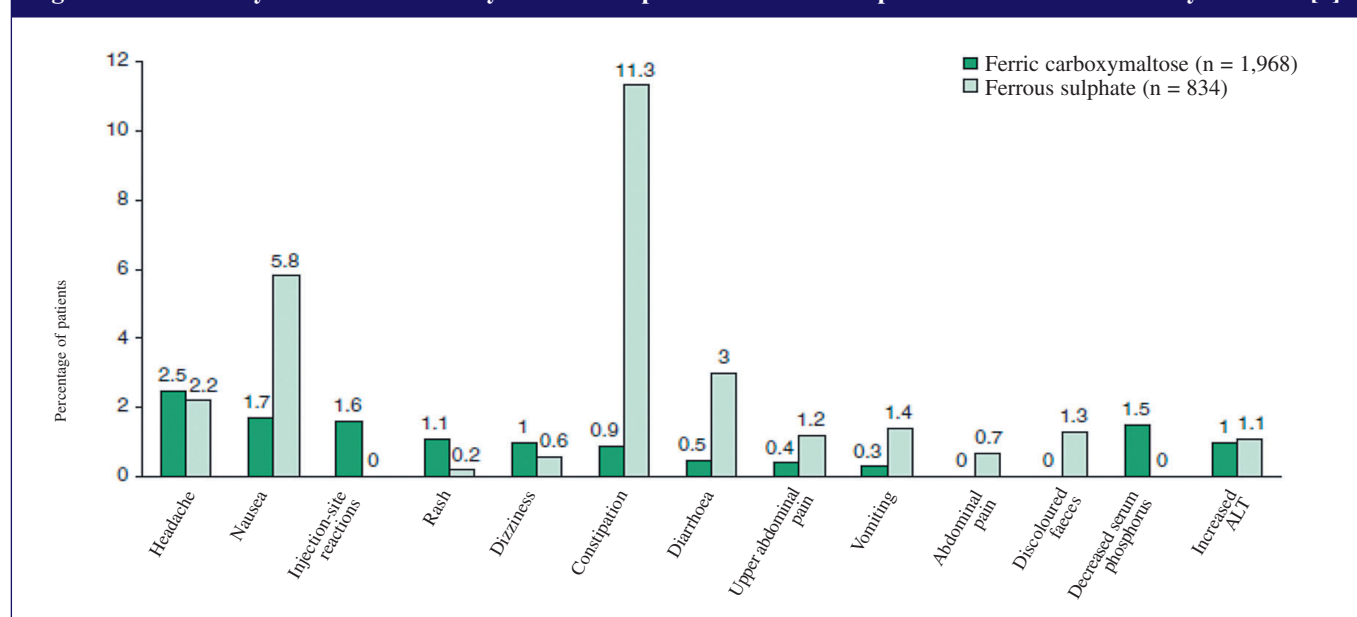
Ferric carboxymaltose is well tolerated with a low incidence of side effects as demonstrated during several clinical trials in patients with iron deficiency anaemia in different clinical settings. Most side effects were considered mild

to moderate with a low proportion of patients discontinuing treatment [14]. The most commonly reported adverse reactions were headaches, nausea, injection site reactions, decreased serum phosphorus, and rash, all below 3% (see Figure 2). Although deaths that occurred during clinical trials were unlikely related to the administration of ferric carboxymaltose, the FDA has requested further safety data from additional clinical studies [7, 15, 16]. In Europe, the product has been registered and launched in several countries and the use of ferric carboxymaltose has gained widespread acceptance. Further regulatory submissions and reimbursement negotiations with the national health authorities are ongoing to improve patient access.

Ferric carboxymaltose in the treatment of iron deficiency anaemia Rapid Hb-response and increase in ferritin levels

The effectiveness of IV ferric carboxymaltose has been demonstrated in several randomised, multicentre, phase III trials in patients with iron deficiency anaemia as a consequence of inflammatory bowel disease, heavy uterine bleeding, postpartum iron deficiency, and chronic kidney disease, mostly with oral iron as active comparator [17-21]. In general, ferric carboxymaltose led to a faster increase

Figure 2: Tolerability of IV ferric carboxymaltose compared to oral iron in patients with iron deficiency anaemia [7]



Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. *Drugs*. 2009;69(6):739-56. Printed with permission by Wolters Kluwer.

in haemoglobin levels compared to oral iron treatment and also increased ferritin levels, indicating successful replenishment of iron stores and improved quality of life and fatigue scores as measured by quantitative surveys. Patients who received ferric carboxymaltose to treat severe, absolute iron deficiency anaemia due to conditions such as abnormal uterine bleeding showed more rapid correction of iron depletion, iron-deficient erythropoiesis, and anaemia with fewer adverse gastrointestinal symptoms, than did patients assigned to oral ferrous sulphate treatment [21]. These data indicate that ferric carboxymaltose, unlike ferrous sulphate, corrects anaemia while also serving as an efficient source to replete physiological iron stores. Ferric carboxymaltose may also prove its value in the treatment of functional iron deficiency that is often associated with anaemia of chronic disease [7].

Functional iron deficiency (FID)

FID occurs when the demand for iron exceeds the amount of iron that can be effectively mobilised from macrophages and from iron stores [1]. FID is common under chronic inflammatory conditions such as inflammatory bowel disease, chronic kidney disease, and congestive heart failure. In patients affected by these clinical conditions, the release of iron from macrophages, from

the intra-cellular iron stores, and from the intestinal mucosa is impaired, which may result in anaemia in spite of filled iron stores. FID is also a particular problem when ESAs are used in conditions like chemotherapy-induced anaemia. Treatment with ESAs typically requires 50 mg of iron per day (instead of 20–25 mg under normal conditions) to keep up with the increase in red blood cell production [8, 22]. However, ESAs are often used in clinical settings with underlying inflammatory conditions where iron is trapped in the macrophages, cannot be released from the stores and its dietary uptake is impaired. Accordingly, the increased iron demand often cannot be met, thus leading to impaired red blood cell production with an increased percentage of hypochromic cells [1]. Accordingly, FID may contribute to the high proportion of patients, up to 50%, with chemotherapy-induced anaemia who do not respond to ESAs [23].

IV iron in combination with ESAs

Because of the efficient delivery of usable iron directly to the bone marrow, IV iron can play a vital role in treating chemotherapy-induced anaemia when used in combination with ESAs. Several randomised studies have shown that ESAs were more effective when used with IV iron than with oral iron formulations alone [23, 24]. Based on these

promising results, further studies with ferric carboxymaltose are scheduled to investigate the optimal use of IV iron in other conditions such as solid tumours and lymphoproliferative diseases [7].

Ferric carboxymaltose – a cost-saving treatment for anaemia

Total administration costs

In addition to its efficacy and improved side effect profile over alternatives, the reduced administration costs make ferric carboxymaltose a cost-effective option [25]. Even though ferric carboxymaltose is the IV iron with the highest drug cost, the simplified handling procedure and short infusion time yield substantial savings (see Figure 3).

Single high-dose administration

Ferric carboxymaltose is a more stable complex than iron gluconate and iron sucrose and allows for administration of high single doses of iron [1]. Despite the improved stability of iron sucrose compared to iron gluconate, both have to be administered at lower dosages than ferric carboxymaltose, requiring more interventions for the patient and doctor. Although the pharmacoeconomic studies looking at cost-effectiveness were performed in Switzerland, similar savings may be possible in other countries due to the decrease in costs to the health-care system associated with fewer infusions (see Figure 3) [25, 26].

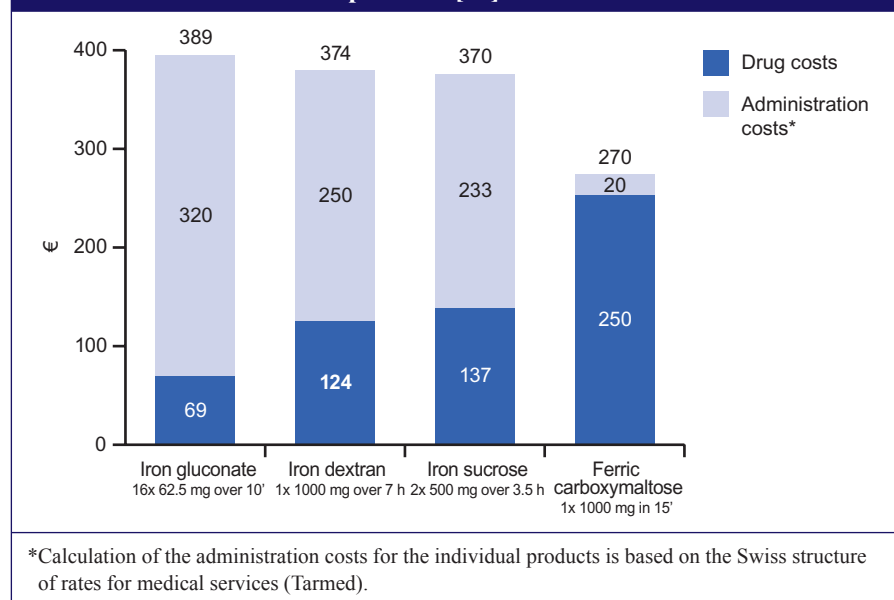
ESA sparing potential

When ferric carboxymaltose is used with ESAs for chronic kidney disease and chemotherapy-induced anaemia, there may be additional economic advantages. Intravenous iron reduces the dose of ESAs required to achieve the target haemoglobin level. In patients with cancer-related anaemia, a Swedish study showed that total costs per patient over 16 weeks of treatment were reduced by 11% when a combined epoetin beta/iron sucrose protocol was used as compared with epoetin beta alone [27, 28].

Conclusion

Ferric carboxymaltose, the next-generation IV iron formulation, is currently indicated for the treatment of iron deficiency when oral iron preparations are not tolerated, ineffective, or cannot be used.

Figure 3: Calculation of total administration costs for 1,000 mg iron by individual IV iron products [25]



Compared to ferric gluconate and iron sucrose, it is a more stable complex allowing for rapid administration of high doses of iron. Given the rapid haemoglobin response when used in conjunction with erythropoiesis-stimulating agents, further indications may be on the horizon. Additional studies are ongoing to further investigate the role of ferric carboxymaltose in the treatment of chemotherapy-induced anaemia and other chronic conditions. Ferric carboxymaltose offers the opportunity for single, high-dose IV infusions with substantial cost saving potential.

References

- Crichton RR, Danielson BG, Geisser P. Iron therapy with special emphasis on intravenous administration. 4th edition. London, Boston: International Medical Publishers; 2008.
- Benoist B, et al, editors. Worldwide prevalence of anaemia 1993–2005. WHO global database of anaemia. World Health Organization; 2008.
- Ross J, Horton S. Economic consequences of iron deficiency. Micronutrient Initiative (Association). Ottawa, Canada; 1998.
- Lozoff B, Beard J, Connor J, et al. Long-lasting neural and behavioral effects of iron deficiency in infancy. *Nutr Rev*. 2006; 64(5 Pt 2):S34-43; discussion S72-91.
- Haas JD, Brownlie T. Iron deficiency and reduced work capacity: a critical review of the research to determine a causal relationship. *J Nutr*. 2001;131(2S-2):676S-88S; discussion 688S-90S.
- Clark SF. Iron deficiency anemia: diagnosis and management. *Curr Opin Gastroenterol*. 2009;25(2):122-8.
- Lyseng-Williamson KA, Keating GM. Ferric carboxymaltose: a review of its use in iron-deficiency anaemia. *Drugs*. 2009;69(6):739-56.
- Huch R, Schaefer R. Iron deficiency and iron deficiency anaemia. New York: Thieme Medical Publishers; 2006.
- Baillie GR, Clark JA, Lane CE, et al. Hypersensitivity reactions and deaths associated with intravenous iron preparations. *Nephrol Dial Transplant*. 2005;20(7):1443-9.
- Chertow GM, Mason PD, Vaage-Nilsen O, et al. On the relative safety of parenteral iron formulations. *Nephrol Dial Transplant*. 2006;21(2):378-82.
- Geisser P. The pharmacology and safety profile of ferric carboxymaltose (Ferinject®): structure/reactivity relationships of iron preparations. *Port J Nephrol Hypert*. 2009; 23(1):11-6.
- Beshara S, Sørensen J, Lubberink M, et al. Pharmacokinetics and red cell utilization of ⁵²Fe/⁵⁹Fe-labelled iron polymaltose in anaemic patients using positron emission tomography. *Br J Haematol*. 2003;120(5): 853-9.
- Ganzoni AM. Intravenous iron-dextran: therapeutic and experimental possibilities. *Schweiz Med Wochenschr*. 1970;100(7):301-3.
- Quinbi W, Benjamin J. Safety and tolerability profile of ferric carboxymaltose (FCM), a new high dose IV iron, across ten multicentre clinical trials. Poster no: MP383. XLV ERA-EDTA Congress. 10-13 May 2008; Stockholm, Sweden.
- Food and Drug Administration Center for Drug Evaluation and Research. Summary Minutes of the Drug Safety and Risk Management Advisory Committee, February 1, 2008 [cited 2009 September 7]. Available from: <http://www.fda.gov/ohrms/docketsac/08/minutes/2008-4337m1-Final.pdf>
- US National Institutes of Health. ClinicalTrials.gov [cited 2009 September 7]. Available from: <http://www.clinicaltrials.gov>
- Kulnigg S, Stoinov S, Simanekov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. *Am J Gastroenterol*. 2008;103(5):1182-92.
- Tagboto S, Cropper L, Turner J, et al. The efficacy of a single dose of intravenous ferric carboxymaltose (Ferinject) on anaemia in a pre-dialysis population of chronic kidney disease patients. *J Ren Care*. 2009; 35(1):18-23.
- Seid MH, Derman RJ, Baker JB, et al. Ferric carboxymaltose injection in the treatment of postpartum iron deficiency anemia: a randomized controlled clinical trial. *Am J Obstet Gynecol*. 2008;199(4):435.e1-7.
- Van Wyck DB, et al. Large-dose intravenous ferric carboxymaltose injection for iron deficiency anemia in heavy uterine bleeding: a randomized, controlled trial. *Transfusion*. 2009; epub ahead of print doi 10.1111/j.1537-2995.2009.02327.x.
- Van Wyck DB, Martens MG, Seid MH, et al. Intravenous ferric carboxymaltose compared with oral iron in the treatment of postpartum anemia: a randomized controlled trial. *Obstet Gynecol*. 2007;110(2 Pt 1):267-78.
- Eschbach JW, Egrie JC, Downing MR, et al. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med*. 1987;316(2):73-8.
- Shord SS, Hamilton JM Jr, Cuellar S. Parenteral iron with erythropoiesis-stimulating agents for chemotherapy-induced anemia. *J Oncol Pharm Pract*. 2008;14(1):5-22.
- Hedenus M, Birgegård G. The role of iron supplementation during epoetin treatment for cancer-related anemia. *Med Oncol*. 2009; 26(1):105-15.
- Szucs TD, Blank P, Schwenkglens M. Health economic impact of intravenous iron supplementation in anaemia treatment with erythropoiesis-stimulating agents. Institute of Social and Preventive Medicine, University of Zurich, Switzerland; European Center of Pharmaceutical Medicine, University of Basel, Switzerland. Poster 0135 at 14th EHA congress 2009; *Haematologica*. 2009; 94(s2):52.
- Steiner S, Brock E, Schneider H, et al. Budget impact (BI) of parenteral iron treatment of iron deficiency anaemia (IDA) in Switzerland. Abstract no. PHM2. *Value Health*. 2007;10(6):A280.
- Hedenus M, Birgegård G, Näsman P, et al. Addition of intravenous iron to epoetin beta increases hemoglobin response and decreases epoetin dose requirement in anemic patients with lymphoproliferative malignancies: a randomized multi-center study. *Leukemia*. 2007;21(4): 627-32.
- Hedenus M, Näsman P, Liwing J. Economic evaluation in Sweden of epoetin beta with intravenous iron supplementation in anaemic patients with lymphoproliferative malignancies not receiving chemotherapy. *J Clin Pharm Ther*. 2008;33(4):365-74.