Iron Status and Analysis of Efficacy and Safety of Ferric Carboxymaltose Treatment in Patients with Inflammatory Bowel Disease

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Key Words
Iron deficiency · Anemia · Anemia of chronic disease · Ferric carboxymaltose · Inflammatory bowel disease · Crohn’s disease · Ulcerative colitis · Ferritin · Iron supplementation

Abstract
Background and Aims: We analyzed iron deficiency and the therapeutic response following intravenous ferric carboxymaltose in a large single-center inflammatory bowel disease (IBD) cohort. Methods: 250 IBD patients were retrospectively analyzed for iron deficiency and iron deficiency anemia. A subgroup was analyzed regarding efficacy and side effects of iron supplementation with ferric carboxymaltose. Results: In the cohort (n = 250), 54.4% of the patients had serum iron levels ≤ 60 μg/dl, 81.2% had ferritin ≤ 100 ng/ml, and 25.6% had hemoglobin (Hb) of ≤ 12 g/dl (females) or ≤ 13 g/dl (males). In the treatment subcohort (n = 80), 83.1% of the patients had iron ≤ 60 μg/dl, 90.4% had ferritin ≤ 100 ng/ml, and 66.7% had Hb ≤ 12/13 g/dl before ferric carboxymaltose treatment. After a median dose of 500 mg ferric carboxymaltose, 74.7% of the patients reached iron > 60 μg/dl, 61.6% had ferritin > 100 ng/ml, and 90.7% reached Hb > 12/13 g/dl at follow-up (p < 0.0001 for all parameters vs. pretreatment values). The most frequent adverse event was a transient increase of liver enzymes with male gender as risk factor (p = 0.008, OR 8.62, 95% CI 1.74–41.66). Conclusions: Iron deficiency and anemia are frequent in IBD patients. Treatment with ferric carboxymaltose is efficacious, safe and well tolerated in iron-deficient IBD patients.

Introduction
Iron deficiency is common in patients with inflammatory bowel disease (IBD), affecting up to 80% of all patients and leading to anemia in approximately one third of all IBD patients [1, 2]. In IBD, iron deficiency is caused by dietary restrictions, iron malabsorption due to active disease or intestinal blood loss. Moreover, the chronic intestinal inflammation in IBD patients leads to an upregulation of proinflammatory cytokines (e.g. IL-1β, IL-6) and consecutively hepcidin, which results in an impaired absorption of iron. Parts of this work were presented as a poster at the 6th Congress of the European Crohn's and Colitis Organization (ECCO) in Dublin 2011 and published in J Crohns Colitis 2011;5(1):S116. This work contains parts of the unpublished medical degree thesis of B. Löhr.
intestinal iron uptake from the gut and sequestering of iron in the reticuloendothelial system. Hepcidin inhibits iron uptake by interaction with the iron export protein ferroportin, which is located on the cell surface of hepatocytes, macrophages and the basolateral membrane of enterocytes [3–5]. This mechanism represents a major cause of iron deficiency and associated anemia of chronic disease in IBD and other chronic inflammatory diseases [6].

For the treatment of iron deficiency anemia, the preferred route of iron supplementation in IBD is intravenous, although many patients would also respond to oral iron. However, intravenous iron is more effective, better tolerated, and improves the quality of life to a greater extent than oral iron supplements. Absolute indications for intravenous iron include severe anemia (Hb <10 g/dl), intolerance, or inappropriate response to oral iron, severe intestinal disease activity, concomitant therapy with erythropoietin, or patient preference. Oral iron supplements can be used if absolute indications for intravenous iron therapy are not met and the response and tolerance should be monitored, and treatment should be changed to intravenous iron preparations if necessary. Several clinical trials clearly demonstrated that intravenous iron supplementation has better efficacy, tolerability and long-term response than oral iron treatment [7–9]. Furthermore, in animal models, there is evidence that oral iron supplements lead to oxidative stress in the gut and may aggravate disease activity [10, 11]. These observations have also been made in IBD patients [12, 13].

Ferric carboxymaltose (Ferinject®, Vifor Pharma, Glattbrugg, Switzerland) is a novel, optimized iron formulation for intravenous application. It is a water-soluble, macromolecular iron hydroxy-complex consisting of polynuclear iron (III) hydroxide with a molecular weight of 150 kDa. Efficacy of ferric carboxymaltose has been demonstrated in various studies, including treatment of anemia in chronic kidney disease, chronic heart failure, post-partum anemia and IBD [14–19]. In the latter trial, ferric carboxymaltose was non-inferior to oral administered ferrous sulfate in terms of hemoglobin (Hb) change over 12 weeks. However, there was superiority in providing a faster Hb response, a higher increase in iron stores, and a better patient tolerance [14]. There are additional advantages of ferric carboxymaltose in clinical practice. For instance, high doses of iron can be administered in a short infusion time (max. 1,000 mg as infusion in 15 min; up to 200 mg as i.v. bolus). Even the risk of side effects regarding toxicity and hypersensitivity seems to be lower compared with other intravenous iron formulations [20].

Therefore, ferric carboxymaltose has been used in our outpatient clinic for the treatment of iron deficiency and iron deficiency anemia since its approval in Germany in November 2007.

Given that all large trials using ferric carboxymaltose were pharmaceutical company sponsored resulting in potential conflicts of interest, we aimed in this study without pharmaceutical sponsoring to analyze the iron status in IBD patients and to investigate the efficacy and safety of ferric carboxymaltose for iron supplementation in IBD patients in clinical practice in a large single-center cohort.

Materials and Methods

Study Cohort

Medical and laboratory records of all patients, who visited our IBD center for the first time in 2008 (n = 250), were analyzed for iron parameters, including serum iron, serum ferritin and Hb values. Iron values of ≤60 µg/dl and ferritin ≤100 ng/ml were considered as clinically relevant and defined as pathologic in this study. According to the WHO definition, anemia is defined as a decline in blood hemoglobin to a concentration of <12 g/dl (120 g/l) in women and of <13 g/dl (130 g/l) in men. Therefore, these values were considered pathologic in this study.

Out of this cohort, we identified 80 patients who were treated with ferric carboxymaltose at least for one dose of 100 mg. Indications for ferric carboxymaltose treatment were serum iron levels of ≤60 µg/dl and Hb ≤12/13 g/dl, or iron ≤60 µg/dl, ferritin ≤100 ng/ml and Hb ≤12/13 g/dl. Patients were also included into the study when serum iron was ≤60 µg/dl and ferritin >100 ng/ml if there was presence of inflammation (elevated CRP and/or elevated leukocyte count without previous or ongoing steroid treatment).

Based on the protocol of the FERGIcor trial [21], the initial ferric carboxymaltose dose was at least 500 mg. Only in 1 patient with allergies against other intravenous iron supplements was an initial dose of 100 mg ferric carboxymaltose chosen. The total ferric carboxymaltose dose (range 100–7,500 mg) was dependent on the severity of the initial iron deficiency and iron deficiency anemia. Efficacy regarding increase of Hb, iron and ferritin and side effects of ferric carboxymaltose treatment, including laboratory values (blood count, liver enzymes and LDH), were monitored. Patients were followed up for a median time interval of 20 weeks. After this study interval, patients with relapsing iron deficiency or iron deficiency anemia (as defined in this study) received further treatment with ferric carboxymaltose.

Statistical Analysis

Data were summarized by adequate measures of location and spread for continuous variables and by proportions for discrete variables. Adequate two-sample tests for continuous data (t test, Mann-Whitney U test) and for discrete data (χ² tests, Fisher’s exact test) were used. For the prediction of liver enzyme elevation, we used a logistic regression model where predictors were selected from a potential set of predicting variables (serum iron, ferritin,
serum CRP, age, duration of IBD, gender, type of IBD (Crohn's disease or ulcerative colitis), body mass index (BMI), concomitant treatment with immunosuppressive agents or anti-TNF antibodies by relying on the multivariate fraction polynomials (mfp) algorithm which simultaneously allows for testing non-linear relationships of continuous predictors and the outcome. To identify patient groups with the greatest risk for anemia, we used a logistic regression model similar to the previous one including all patients with iron deficiency anemia (excluding patients with macrocytic anemia) and anemia Hb levels ≤12/13 g/dl as outcome predictor. The corresponding set of potential predictors was serum iron, ferritin, serum CRP, age, gender, type of IBD, disease duration, BMI, concomitant treatment with immunosuppressives or anti-TNF antibodies and MCV. For predicting ferritin, we built a linear regression model by relying on the mfp algorithm where the potential predictors gender, iron, CRP, Hb and BMI were considered. To satisfy the normality assumption, we took the natural logarithm of ferritin for modeling purposes. Using the same method, we developed a model for predicting Hb from the potential predictors ferritin, CRP, iron and gender. Based on the final linear regression model for Hb, we were able to construct prediction intervals for an individual case’s Hb value given the values of the selected predictors. Further, the assumptions of the regression models were evaluated by using graphically based residual analyses. All statistical tests were performed two-sided, a p value of <0.05 was considered as statistically significant. All statistical analyses were performed by using R (version 2.12.1) and PASW Statistics 17.0.

**Results**

**Prevalence of Iron Deficiency and Iron Deficiency Anemia in IBD Patients**

Iron parameters and Hb levels of 250 IBD patients, who visited our IBD center for the first time from January 2008 to December 2008, were analyzed. Crohn’s disease was diagnosed in 67.6% (n = 169), ulcerative colitis in 32.4% (n = 81); 55.6% (n = 139) were females, 44.4% (n = 111) were males. There was a high prevalence of iron deficiency among these patients. Serum iron levels of ≤60 μg/dl were seen in 136 patients (54.4%), 203 patients (81.2%) had ferritin levels ≤100 ng/ml and 64 patients (25.6%) were anemic with Hb levels ≤12/13 g/dl (table 1). Iron deficiency anemia with iron values ≤60 μg/dl, ferritin levels ≤100 ng/ml and Hb levels ≤12/13 g/dl were found in 44 patients (17.6%). In this study, we defined Hb levels ≤12/13 g/dl as anemia of chronic disease, when concomitantly serum ferritin levels were ≥100 ng/ml and CRP serum levels were >0.5 mg/dl. Only 9 patients (3.6%) met these criteria.

**Predictors of Microcytic Anemia in IBD Patients**

Multivariate logistic regression analyses demonstrated a stronger effect of serum iron than ferritin levels on the prediction of microcytic anemia. This analysis revealed (logarithmized) serum iron (p < 2.38 × 10^–10) with an odds ratio (OR) of 0.03 [95% confidence interval (CI) 0.01–0.09] and (logarithmized) ferritin (p = 1.25 × 10^–4) with an OR of 0.29 (95% CI 0.15–0.55) as risk factors for the development of microcytic anemia.

Ferritin levels are modulated by the degree of inflammation (as reflected by CRP values). Similarly, in our study cohort, ferritin levels were significantly influenced by the (logarithmized) serum CRP levels (p = 0.005). A final linear regression model applied to our IBD study population (n = 250) statistically confirmed the effect of iron (p < 0.001) on Hb. As expected, gender also showed statistically significant differences in predicting Hb levels (p < 0.001) with higher Hb values in males. Additionally, the mfp algorithm revealed a non-linear relationship between iron and Hb as shown in figure 1. For predicting the mean Hb value based on serum iron level (labeled in the formula as ‘iron’) and gender, the linear predictor of the final regression model can be used which is given by:

**Male IBD patients:** $Hb = 17.45 - 19.07 \times \sqrt[3]{\text{iron}}$

**Female IBD patients:** $Hb = 17.45 - 19.07 \times \sqrt[3]{\text{iron}} - 0.8$

The corresponding 50 and 95% Hb prediction intervals based on serum iron levels are shown in figure 2a and b separately for male and female IBD patients. The percentiles in these figures may be helpful for deciding when intravenous iron supplementation should be started; however, considering the high variability of serum iron levels, these figures cannot replace more reliable param-

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**Table 1. Demographic and clinical characteristics of the whole study cohort (n = 250)**

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>111/139 (44.4/55.6)</td>
</tr>
<tr>
<td>Median age, years</td>
<td>36.9 (18–74)</td>
</tr>
<tr>
<td>CD/UC</td>
<td>169/81 (67.6/32.4)</td>
</tr>
<tr>
<td>Median duration of disease, years</td>
<td>8 (2–38)</td>
</tr>
<tr>
<td>Iron ≤60 μg/dl</td>
<td>136 (54.4)</td>
</tr>
<tr>
<td>Ferritin ≤100 ng/ml</td>
<td>203 (81.2)</td>
</tr>
<tr>
<td>Hb levels ≤12/13 g/dl</td>
<td>64 (25.6)</td>
</tr>
<tr>
<td>CRP &gt;0.5 mg/dl</td>
<td>142 (56.8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients treated with</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunosuppressives</td>
<td>179 (71.6)</td>
</tr>
<tr>
<td>Systemic corticosteroids</td>
<td>56 (22.4)</td>
</tr>
</tbody>
</table>

Values are numbers with percentages or range in parentheses.
Efficacy of Ferric Carboxymaltose Treatment

Out of the whole patient cohort (n = 250), 80 patients were treated with ferric carboxymaltose and were followed up for a median of 20 weeks (range 1–60). In this subgroup, 61.3% had Crohn’s disease (n = 49), 38.7% ulcerative colitis (n = 31), 56.2% (n = 45) were females and 43.8% (n = 35) were males. Total cumulative ferric carboxymaltose doses during the follow-up period ranged from 100 to 7,500 mg (see details in the Materials and Methods section). The median dose was 500 mg (table 2).

Seventy-one patients had complete data on iron parameters and Hb levels to be analyzed for efficacy of ferric carboxymaltose treatment. Before treatment with ferric carboxymaltose, 83.1% of the patients (n = 59) had serum iron levels of ≤60 μg/dl, while only 16.9% of the patients had normal serum iron levels. In the follow-up period and after a median dose of 500 mg ferric carboxymaltose, 74.6% (n = 53) reached the target serum iron level of >60 μg/dl (fig. 3a; p < 0.001) versus pretreatment levels.

Ferritin levels were analyzed in 73 patients treated with ferric carboxymaltose. Before treatment with ferric carboxymaltose, 90.4% of the patients (n = 66) had serum ferritin ≤100 ng/ml, while only 9.6% had ferritin values >100 ng/ml. In the follow-up period and after a median

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**Table 2. Demographic and clinical characteristics of the subcohort with ferric carboxymaltose treatment (n = 80)**

<table>
<thead>
<tr>
<th>Demographic and clinical characteristics</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n (%)</td>
<td>35/45 (43.8/56.2)</td>
</tr>
<tr>
<td>Median age, years (range)</td>
<td>35.2 (18–70)</td>
</tr>
<tr>
<td>CD/UC, n (%)</td>
<td>49/31 (61.3/38.7)</td>
</tr>
<tr>
<td>Median duration of disease, years (range)</td>
<td>7 (2–30)</td>
</tr>
<tr>
<td>Median dose of ferric carboxymaltose, mg (range)</td>
<td>500 (100–7,500)</td>
</tr>
<tr>
<td>Median follow-up, weeks (SD)</td>
<td>20 (12)</td>
</tr>
<tr>
<td>Iron ≤60 μg/dl, n (%)</td>
<td>59 (83.1)</td>
</tr>
<tr>
<td>Ferritin ≤100 ng/ml, n (%)</td>
<td>66 (90.4)</td>
</tr>
<tr>
<td>Hb levels ≤12/13 g/dl, n (%)</td>
<td>50 (66.7)</td>
</tr>
<tr>
<td>CRP &gt;0.5 mg/dl, n (%)</td>
<td>39 (48.8)</td>
</tr>
<tr>
<td>Anti-TNF-α antibody-treated patients, n (%)</td>
<td>59 (73.7)</td>
</tr>
<tr>
<td>Patients treated with</td>
<td></td>
</tr>
<tr>
<td>Immunosuppressives, n (%)</td>
<td>46 (57.5)</td>
</tr>
<tr>
<td>Systemic corticosteroids, n (%)</td>
<td>4 (5.0)</td>
</tr>
</tbody>
</table>

CD/UC = Crohn’s disease/ulcerative colitis.
Iron Status and Ferric Carboxymaltose Treatment in IBD

dose of 500 mg ferric carboxymaltose, 61.6% (n = 45) reached the ferritin target value of >100 ng/ml (fig. 3b; p < 0.001) versus pretreatment levels.

Seventy-five patients were analyzed regarding changes of Hb levels under ferric carboxymaltose treatment. Before treatment, 66.7% of the patients (n = 50) had Hb levels ≥12/13 g/dl, while only one third (33.3%; n = 25) had normal Hb levels. After a median dose of 500 mg ferric carboxymaltose, 90.7% (n = 68) reached Hb levels ≥12/13 g/dl in the follow-up period (fig. 3c; p < 0.001) versus pretreatment levels.

Side Effects of Ferric Carboxymaltose

During the median follow-up period of 20 weeks, 17.5% of the patients (n = 14) developed side effects associated with ferric carboxymaltose treatment. The most frequent adverse event was a transient increase of liver enzymes (APT and/or ALT) of greater than two times the upper normal limit, which occurred in 12 patients (15.0%) and completely resolved at follow-up. One patient complained about headaches after the infusion (1.25%) and 1 patient developed feet edema (1.25%; table 3).

Predictors of Abnormal Liver Function Tests in Ferric Carboxymaltose-Treated IBD Patients

Given that a transient increase of liver enzymes was the most frequent side effect of ferric carboxymaltose treatment within the follow-up period, we aimed to identify predictors for the development of increased liver enzymes using multivariate analysis and pretreatment parameters (γ-GT, Hb, serum iron levels, ferritin, CRP) and age, gender, type of IBD (Crohn’s disease or ulcerative colitis), BMI, concomitant treatment with immunosuppressives or anti-TNF antibodies and cumulative dose ferric carboxymaltose as predictor variables. Multivariate analyses revealed only male gender (p = 0.008, OR 8.621, 95% CI 1.74–41.66) as risk factor for the development of increased liver enzymes.

Discussion

In our single-center cohort, we found a high prevalence of iron deficiency and anemia, which is consistent with findings of other studies in IBD patients [1, 2, 22]. Given that anemia is the most common systemic compli-

Fig. 3. Percentages of patients with iron values >60 and ≤60 μg/dl (a), ferritin values >100 and ≤100 mg/dl (b), and Hb values >12/13 and ≤12/13 g/dl (c) before ferric carboxymaltose treatment (preFCM) and at follow-up after a median dose of 500 mg ferric carboxymaltose.

<table>
<thead>
<tr>
<th>Side effect</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase of liver enzymes</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (1.25)</td>
</tr>
<tr>
<td>Feet edema</td>
<td>1 (1.25)</td>
</tr>
</tbody>
</table>

Table 3. Side effects in the ferric carboxymaltose treatment group (n = 80)
cation in IBD patients, treatment of iron deficiency, which is the major cause for anemia in these patients, is an important goal in IBD treatment [23–25]. In our patient cohort, iron, ferritin and Hb restorage was achieved with a median dose of 500 mg ferric carboxymaltose in the majority of the patients with very low side effects. The most frequent side effect was a transient increase of liver enzymes, particularly in male patients.

The present study was limited by the lack of sufficient data for most patients regarding transferrin saturation and soluble transferrin receptor, which are important laboratory parameters of iron status in patients with systemic inflammation, in which serum ferritin levels may be increased despite iron deficiency [26]. Similarly, in our IBD cohort, ferritin levels were significantly modulated by the serum CRP levels. Using a linear regression model, we demonstrate a non-linear relationship between iron and Hb. In addition, we provide Hb percentile curves based on the serum iron levels which may be a helpful tool for deciding when intravenous iron supplementation should be started in IBD patients. However, we have to acknowledge that serum iron levels are influenced by a number of factors and are much less reliable than transferrin saturation or soluble transferrin receptor.

In the past, oral iron supplementation has been commonly used in IBD patients. While oral iron supplementation is suitable and effective in patients without malabsorption, side effects like nausea and constipation and insufficient restorage of iron and Hb levels limit the use of oral iron formulations. In addition, several studies demonstrated that oral iron induces oxidative stress in the gut and aggravates inflammation [11, 27]. In IBD patients, there is often the need for high iron doses due to very low iron stores, resulting from chronic bleeding or inflammatory conditions [2, 28, 29].

For administration of high iron doses, most approved intravenous formulations like low or high molecular weight iron dextran, iron sucrose and sodium ferric gluconate have to be given several times with long infusion times to reach target iron/Hb values. In addition, several of these agents, particularly high molecular weight iron dextran, may have side effects like severe anaphylactic reactions.

Ferric carboxymaltose, a novel iron formulation, was approved for treatment of iron deficiency and iron deficiency anemia in Europe in 2007. Several studies in patients with different disease entities demonstrated improved symptoms, functional capacity and quality of life, while the side-effect profile was acceptable [14, 15, 30, 31].

In this study, the initial ferric carboxymaltose dose was based on data of the randomized controlled FERGICOR trial [21], in which all patients received initially at least 500 mg ferric carboxymaltose. This simpler ferric carboxymaltose-based dosing regimen showed better efficacy and compliance compared with the Ganzoni-calculated iron sucrose dose regimen [21]. Our results support the data of the FERGICOR trial [21] and demonstrate that in the majority of patients encountered in daily practice, a single 500 mg ferric carboxymaltose infusion is sufficient to treat iron deficiency and mild iron deficiency anemia.

Although comparative studies analyzing efficacy are rare, there are data regarding side effects. In a clinical trial including patients with chronic kidney disease undergoing hemodialysis, a lower proportion of ferric carboxymaltose than iron sucrose recipients experienced at least one drug-related adverse event (5 vs. 10.2%; p value not reported). However, there were no statistically significant differences between the groups regarding other parameters of drug tolerability [32]. The tolerability and safety profile of ferric carboxymaltose has been summarized in an abstract which included ten studies with >2,000 patients treated with ferric carboxymaltose [33]. According to this summary, 15.3% of ferric carboxymaltose recipients and 26.1% of oral ferrous sulfate recipients reported at least one drug-related adverse event. Headache, the most frequently reported adverse event related to ferric carboxymaltose, occurred in <3% of patients of both treatment groups which is consistent with our study, in which only 1 patient (1.2%) complained about headaches after therapy. Rash and local injection site reactions were more common in patients treated with ferric carboxymaltose, whereas gastrointestinal adverse events (particularly constipation and nausea) were more frequently reported in ferrous sulfate recipients across the trials [20]. The very recently released data of the FERGICOR trial [21] demonstrate that hyperferritinemia and transient hypophosphatemia may be an additional side effect of ferric carboxymaltose treatment.

Toxicity of iron treatment is well known. The concentration of non-transferrin-bound iron/free iron has been shown to correlate with an increase in the incidence of adverse events following intravenous administration of iron sucrose [34]. It has been proposed that non-transferrin-bound iron may catalyze a number of reactions that in turn lead to oxidative stress and membrane damage.

As a mechanism of iron deficiency, hepcidin represents a key regulator of iron metabolism. When using po-
tent anti-inflammatory drugs like anti-TNF antibodies, hepcidin may be downregulated. This in turn leads to an increased iron mobilization and uptake from the gut [35], which may result in a functional increase in iron deficiency. To treat the higher demand for iron in this situation, transitional high-dose iron supplementation is necessary [36]. Hence, by the early use of highly effective anti-inflammatory therapeutics (i.e. anti-TNF antibodies) in IBD patients with the goal of mucosal healing, long-term incidence of iron deficiency may decrease in the future [37].

In summary, iron deficiency and anemia are very common in IBD patients. As we demonstrated in our study, ferric carboxymaltose is a very efficient and well-tolerated therapy in IBD patients. In this cohort, transient liver enzyme elevations were the most common side effect. A single dose of 500 mg ferric carboxymaltose was sufficient to normalize Hb levels in the majority of iron-deficient IBD patients. Limitations of this study include its retrospective nature and the lack of transferrin saturation levels in the majority of patients. Further prospective studies with larger patient cohorts are needed to clarify the advantages and cost-effectiveness of ferric carboxymaltose compared to other intravenous iron formulations.

Acknowledgements

S. Brand is supported by grants from the Deutsche Forschungsgemeinschaft (DFG; BR 1912/6-1), the Else Kröner-Fresenius-Stiftung (Else Kröner Fresenius-Stiftung 2010; 2010 EKES.32) and by grants from the Ludwig Maximilians University Munich (LMUM; Excellence Initiative – Investment Fund 2008 and FoFoLe Program 2007 and 2008). F. Beigel is supported by grants from LMUM (FoFoeLe Program 2008) and the DFG (BE 4490/2-1). F. Schnitzer is supported by grants from LMUM (FoFoeLe Program 2009). J. Seiderer was supported by grants from LMUM (FoFoeLe Program, Nr. 422; Habilitationsstipendium, LMUEXCELLENT), the Robert Bosch Foundation and the Else Kröner-Fresenius-Stiftung (Else Kröner-Memorial Stipendium 81/08//EKMS08/01).

Disclosure Statement

The authors have no conflicts of interest to declare.

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