State of the iron: How to diagnose and efficiently treat iron deficiency anemia in inflammatory bowel disease

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Abstract

Iron deficiency anemia (IDA) frequently occurs in patients suffering from inflammatory bowel disease (IBD) and negatively impacts their quality of life. Nevertheless, the condition appears to be both under-diagnosed and undertreated. Regular biochemical screening of patients with IBD for anemia by the gastroenterology community has to be advocated. Oral iron is a low cost treatment however its effectiveness is limited by low bioavailability and poor tolerability. Intravenous (IV) iron rapidly replenishes iron stores and has demonstrated its safe use in a number of studies in various therapeutic areas. A broad spectrum of new IV iron formulations is now becoming available offering improved tolerability and patient convenience by rapidly restoring the depleted iron status of patients with IBD. The following article aims to review the magnitude of the problem of IDA in IBD, suggest screening standards and highlight existing and future therapies.

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KEYWORDS
Anemia; Crohn's disease; Iron deficiency; Inflammatory bowel disease

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Abbreviations: ACD, Anemia in chronic disease; CD, Crohn's disease; CDK, Chronic kidney disease; CHr, Reticulocyte hemoglobin content; ESA, Erythropoiesis stimulating agent; Hb, Hemoglobin; HMWID, High molecular weight iron dextran; IBD, Inflammatory bowel disease; ID, Iron deficiency; IDA, Iron deficiency anemia; IV, Intravenous; LMWID, Low molecular weight iron dextran; TDI, Total dose infusion; UC, Ulcerative colitis.

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1. Introduction

Anemia is a frequent extra-intestinal manifestation in inflammatory bowel disease (IBD) known to negatively impact physical quality of life. Anemia has been even revealed as a co-morbid condition that contributes to death of patients with IBD. Though it seems logical that anemia would also increase the rate of hospitalization and medical costs in IBD respective data are still lacking.

Iron deficiency (ID) and anemia of chronic diseases (ACD) are the most common causes of anemia in IBD. Therefore, together with an adequate control of underlying inflammation iron replacement therapy should start as soon as ID or anemia is detected to attain a normal iron status and Hb. This results in improvement in the patients’ quality of life independent of changes in disease activity. Although efficient therapeutic options have been developed for the treatment of IBD-associated anemia, treating this manifestation appears to remain of low priority for gastroenterologists.

This review aims to give some guidance on how to address ID in patients with IBD including screening procedures, therapeutic options and their potential outcomes. Furthermore the review discusses potential clinical benefits of a new generation of IV iron preparations in the treatment of IBD.

2. Prevalence and etiology of anemia in IBD

Prevalence rates of anemia in IBD are widely varying from 6 to 74%, which also appears to reflect differences in the standards of screening and treatment as well as in the settings under which patients were studied. Anemia is reported more frequently in hospitalized patients with IBD and occurs more frequently in Crohn’s disease (CD) as compared to ulcerative colitis (UC). It also appears that hemoglobin concentrations increase in the years after diagnosis which may be explained by the remission of disease following successful medical or surgical treatment.

Anemia in IBD is mainly the expression of a mixed pathogenesis with ID and ACD posing the most prominent factors often existing in parallel. Nevertheless, with a reported prevalence of up to 90% ID is the most frequent cause. Iron deficiency may be related to low dietary intake as well as low intestinal bioavailability of iron, decreased internal iron turn-over, and blood loss. Semrin and co-workers suggested that inflammation may inhibit iron absorption as it correlates with disease activity and markers of inflammation in Crohn’s disease. The accurate contribution of intestinal blood loss as a source of ID has not been studied, although it is supposed to pose a major component.

On the other hand, the exact prevalence of ACD is unknown. The etiology of ACD is ascribed to altered erythropoiesis and red cell survival. IBD patients may suffer from functional iron deficiency (FID) due to iron retention in macrophages driven by pro-inflammatory cytokines and hepcidin. During an acute phase response hepcidin is induced in the liver by IL-6 and reduces iron absorption from the duodenum as well as iron recycling from macrophages. In addition, chronic inflammation has been suggested to decrease erythropoiesis either directly by IFN-gamma or because of decrease in the synthesis and the biological activity of erythropoietin (EPO) induced by IL-1, IL-6, TNF-alpha, and hepcidin.

Finally, it must be borne in mind that there are other frequent reasons for anemia in IBD patients. Vitamin B12 deficiency is commonly found in patients with IBD, particularly after resection of the ileum and may lead to hyperchromatosis and macrocytosis. Prescribed medical treatment should also be considered as a potential cause of anemia in patients with IBD. Methotrexate and sulfasalazine interfere with the absorption of folate and may mediate folate deficiency. Sulfasalazine may also induce hemolysis or bone marrow aplasia. Thiopurines and methotrexate can induce bone marrow toxicity in a minority of patients.

3. Clinical manifestations and consequences of iron deficiency

Symptoms and signs of ID even without anemia comprise impaired physical performance, reduced cognitive function, fatigue, headache, dizziness, shortness of breath, restless legs syndrome, hair loss, angular stomatitis, glossitis, pica and reduced libido. Other features include an increase in complications during pregnancy, blunted thermoregulation, and villous atrophy.

IDA in addition has an impact on the immune status and morbidity from infections. ACD is caused by iron retention in macrophages. Phylogenetically this is an interesting and potentially protective innate immune function of the host because iron is a key growth and virulence factor for...
microbes. Iron is also an essential component of many enzymes. Iron is involved in immune effector pathways of neutrophils and macrophages, e.g. formation of toxic hydroxyl radicals. Iron restriction affects B cell and T helper cell proliferation and differentiation, and iron overload leads to NK cell dysfunction. Additionally, high iron reduces the responsiveness of macrophages to IFN-γ resulting in lower production of TNF-α.

Another important aspect is the relationship between ID, thrombocytosis and thromboembolism. It is recognized that there is an increased risk of deep venous thrombosis and thromboembolism in patients with IBD. Indeed this risk in the younger age groups is 3–4 times higher. There is also an increased risk of recurrent thromboembolism and ID independently increases this risk. Thrombocytosis in IBD is a typical feature of active disease and appears to be driven by acute phase responses of interleukins such as IL-6 dependent induction of thrombopoietin and increased levels of IL-11. But iron deficiency in itself may lead to thrombocytosis in IBD due to the expansion of the megakaryocyte lineage and accelerated differentiation. As to whether IDA per se may be linked to an increased risk of thromboembolic events independent of thrombocytosis remains to be determined.

4. Differential diagnosis of anemia in IBD

IBD patients at risk of anemia are typically newly diagnosed patients presenting with high disease activity and possibly bleeding and UC patients with extensive disease. As anemia is the most common extra-intestinal complication in IBD and ID is the most prevalent cause of anemia in IBD, assessment of the iron status is imperative. The World Health Organization defines anemia as a hemoglobin (Hb) concentration <12 g/dL (7.45 mmol/L) in non-pregnant women and <13 g/dL (8.07 mmol/L) in men. These criteria apply also in IBD. However, there is no single biomarker to diagnose ID. Assessment of iron status at a low cost involves simple measurements and allows in most cases differentiating between IDA, ACD and the combination of the two (Table 1).

Basic laboratory screening for anemia in IBD should comprise Hb, full blood counts (including reticulocytes) and assessments of total store of body iron with serum-ferritin (S-ferritin), of the iron available to the bone marrow (erythron) with transferrin saturation (TfS), and of the level of inflammation by means of C-reactive protein (CRP). Further testing for causes of anemia in IBD could comprise vitamin B12, folic acid, haptoglobin, lactate dehydrogenase, and serum creatinine in order to exclude potential hemolysis or renal disease, which in itself causes anemia. Patients in clinical remission should be screened at least every 12 months, whereas patients with active disease at least every 3 months or at shorter intervals depending upon iron status.

4.1. Iron deficiency without anemia

A normal Hb level does not exclude ID, because individuals with normal body iron stores must lose a large portion of body iron before the Hb falls below the laboratory definition of anemia. In non-anemic IBD patients, the most important clinical clue of ID is the symptom of chronic fatigue as iron is required for the enzymes involved in oxidative metabolism. However, as an unspecific symptom it is of little screening value.

A normal Hb level with a mean corpuscular hemoglobin (MCH) in the lower limit of normality (normal range: 28–35 pg) or an increased red cell distribution width (RDW, normal range: 11–15) point to mild ID without anemia. Interestingly, RDW has been reported as an independent indicator for predicting disease activity in patients with CD and UC without anemia. However, in every day clinical practice, the main laboratory finding is a low ferritin level (1 ng/mL of serum ferritin corresponds to approximately 8 mg of stored iron). Thus, measurement of ferritin provides the most useful indirect estimate of body iron stores, and ID can be defined by a ferritin level <30 ng/mL in the absence of inflammation (e.g., normal serum concentrations of C-reactive protein [CRP] and/or normal erythrocyte sedimentation rate). In the presence of inflammation, a normal ferritin level (acute phase reactant) does not exclude ID, and TfS should be also measured. Thus, in the presence of inflammation, functional ID should be defined by low TfS (<20%) and normal ferritin concentrations (>100 ng/mL), whereas low TfS (<20%) and intermediate ferritin values (30–100 ng/mL) suggest absolute ID. Functional ID may also occur in response to the therapeutic use of erythropoiesis stimulating agents, which place a significant demand on iron stores that may surpass the iron-release capacity of the RES.

ID can also be defined by a ferritin index >3.2 (>2.0 if CRP >5 mg/L). The ferritin index is the ratio between the soluble transferrin receptor (sTR; truncated form of the transferrin receptor whose serum concentration is proportional to the total amount of surface transferrin receptors) and the log ferritin, and reflects the iron supply for erythropoiesis. Reticulocyte Hb content (Chr) has also been suggested to be able to differentiate IDA and ACD. It measures the Hb content of reticulocytes and is a direct measure of available iron for erythropoiesis. Chr has a high sensitivity and specificity for diagnosing iron deficiency and is less affected by inflammation than transferrin saturation and ferritin, but so far no data are available from IBD.

4.2. Iron deficiency anemia

Patients should be considered to suffer from IDA when they present with low Hb (men <13 g/dL and women <12 g/dL), TfS (<20%) and ferritin concentrations (<30 ng/mL) but no signs of inflammation. A low mean corpuscular Hb (MCH <27 pg), or better a low reticulocyte Hb content (Chr <28 pg), rather than mean corpuscular (MCV <80 FL) became the most important red cell markers for detecting ID in circulating red blood cells.
Figure 1  Algorithm for diagnosis of iron deficiency anaemia in IBD.

(Fig. 1). MCV is a reliable and widely available measurement but is a relatively late indicator in patients who are not actively bleeding.34 Although sTfR levels are high or very high in uncomplicated IDA, as is the ferritin index, they are not usually required for the diagnosis.34

4.3. Anemia of chronic disease

Patients should be considered to suffer from ACD, also called anemia of inflammation, when they have: 1) evidence of inflammation (e.g. increased serum CRP level) 2) a Hb concentration <13 g/dL for men and <12 g/dL for women, and 3) a low transferrin saturation (TfS <20%), but normal or increased serum ferritin concentration (>100 ng/ml; Fig. 1). In the presence of intermediate serum ferritin concentration (30–100 ng/ml), confirmation of ACD will be given by the ferritin index plot as a sTfR/log ferritin ratio <2 with normal CHr (Table 2).38-41

4.4. Anemia of chronic disease with absolute iron deficiency

Patients should be suspected to have ACD with absolute iron deficiency when they have: 1) a chronic inflammation, 2) a Hb concentration <13 g/dL for men and <12 g/dL for women, and 3) a low transferrin saturation (TfS <20%) with a serum ferritin concentration >30 and <100 ng/ml (Fig. 1). Confirmation of ACD+ID will be given by the ferritin index plot as a sTfR/log ferritin ratio <2 with a CHr <28 pg (Table 2).38-41

Supplementary laboratory tests may need to be taken into consideration for the differential diagnosis between IDA and ACD (Table 2).20,42 Recently, it has been shown that hepcidin levels were significantly higher in IBD patients compared with healthy controls, whereas those of prohepcidin levels were significantly lower.43 In addition, significant correlations of hepcidin with ferritin, CRP and disease activity of IBD were found. This finding suggests a substantial role of these two hormones in the development of anemia in IBD, and the potential role of hepcidin measurement for its differential diagnosis. In this regard, Thomas et al. have shown that hepcidin may replace the ferritin index for confirmation of combined IDA and ACD, which may be given by the hepcidin plot as a hepcidin >4 nmol/L with a CHr <28 pg.44

In addition some hematological indices may help in the diagnosis of iron deficiency in ACD, but which are available in specific hematology analyzers only. Hypochromic red blood cells (Hypo) are reported by the Bayer Advia 120 hematology analyzer (normal value <5%).45 The Sysmex XE-2100 hematology analyzer determines RET-Y, which can be considered the reticulocyte hemoglobin equivalent (RET-He), as well as RBC-Y, which can be considered as the erythrocyte hemoglobin equivalent.46 The clinical utility of these new indices in the diagnosis of ID is currently under evaluation.47 Finally, the Beckman-Coulter LH 780 determines different red cell parameters, such as RDW, Red blood cell Size Factor (RSF), Reticulocyte Distribution Width-Coefficient of Variation (RDWR-CV), and Reticulocyte Distribution Width-Standard Deviation (RDWR-SD). In a recent study, of 100 IBD patients and 102 healthy controls, high values of RDW and low values of RSF were the best markers for the diagnosis of IDA, whereas both RDWR-CV and RDWR-SD were significantly correlated with disease activity and CRP levels.48

5. Treatment options for ID in IBD

The prevalence of anemia in IBD has decreased over time, reflecting the improved treatment modalities for IBD patients.10 However, in IBD patients consecutively seen and who had blood test at an outpatient clinic during the years 1993 and 2003, Vijverman et al. observed that prevalence has only decreased for mild to moderate, but not severe anemia in an IBD population over the last 10 years.49 Therefore, IDA remains a significant clinical problem, which requires careful assessment and management in IBD.6 Unlike nephrologists to whom administration of intravenous (IV) iron has become routine in the management of anemia in patients with chronic kidney disease (CKD), incorporation of iron therapy, particularly in its IV formulations, to the treatment standards in IBD appears to have progressed slowly.8,10 Only recently anemia

Table 2  Laboratory findings in anaemia – supplementary work up.

<table>
<thead>
<tr>
<th>Laboratory measures</th>
<th>IDA</th>
<th>ACID</th>
<th>IDA and ACID</th>
</tr>
</thead>
<tbody>
<tr>
<td>sTfR</td>
<td>↑</td>
<td></td>
<td>↑ or normal</td>
</tr>
<tr>
<td>sTfR-Ferritin index</td>
<td>High (&gt;2)</td>
<td>↓</td>
<td>High (&gt;2)</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>↓</td>
<td>↓ or normal</td>
<td>↓ or normal</td>
</tr>
<tr>
<td>Reticulocyte Hb content (CHr, pg)</td>
<td>&lt;28</td>
<td>≥28</td>
<td>&lt;28</td>
</tr>
<tr>
<td>Percentage of hypochromic red cells</td>
<td>≥5</td>
<td>&lt;5</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Zinc protoporphyrin (μmol/mol heme)</td>
<td>≥40</td>
<td>&lt;40</td>
<td>≥40</td>
</tr>
<tr>
<td>Cytokine levels</td>
<td>Normal</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Hepcidin</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>
has been recognized as an overlooked villain in IBD. This is also reflected by the fact that guidelines for iron therapy were not considered by the initial consensus proceedings from the European Crohn’s and Colitis Organization (ECCO). Very recently, Auerbach and Ballard reviewed the history, pharmacology, administration, efficacy, and toxicity of intravenous iron within the Educational Program of the American Society of Hematology. They clearly showed how intravenous iron offers advantages over oral iron for the treatment of IDA across a wide range of disease states associated with absolute and functional ID. They also discussed the remaining concerns about the acute safety profiles of the available preparations and the potential for long-term toxicity with their repeated administration.

Since parenteral iron was first introduced for human use in the 1930s, much progress and innovation has occurred. Eighty years ago, iron, administered as an oxyhydroxide complex, was toxic. This problem was circumvented with the introduction of compounds containing iron in a core surrounded by a carbohydrate shell, consisting of dextran, gluconate, sucrose, or dextrin. The first dextran-containing IV iron preparations (high molecular weight iron dextran, HMWID), which were introduced in 1954, allowed for large dose administration, but carried a risk of anaphylaxis, which is of less concern with the later introduced low molecular weight iron dextran preparation (LMWID) in 1991. Ferric gluconate (1999) and iron sucrose (2000) were the first available dextran-free iron preparations. Recently, three newer IV iron preparations (ferumoxytol, ferric carboxymaltose and iron isomaltoside 1000) have become available for which a test dose is no longer required and due to the structure of the formulations higher doses of iron can be delivered as a single dose administration. Nevertheless, iron reactions may occur with all IV iron preparations, but are generally not thought to be immune mediated. Table 3 summarizes the characteristics of the available IV preparations.

6. Iron therapy and the course of IBD

Iron supplementation should be considered in all iron deficient patients with IBD and initiated in those in whom hemoglobin concentrations fell below normal (Fig. 2). Because of its low cost and non invasive method of administration oral iron at a daily dose between 50 mg and 200 mg is the conventional approach in patients with mild to moderate anemia (Hb ≥ 10 g/dL, ferritin ≥ 30 μg/L). Oral iron compounds are mostly available as inorganic ferrous salts, sometimes combined with vitamin C which enhances iron absorption. However, gastrointestinal tolerability of oral iron is limited and it may take two to three weeks for hemoglobin concentrations to increase, up to two months to achieve normal values and at least six months to replenish iron stores. In addition to the generally low bioavailability of oral iron, intestinal absorption is further compromised in patients with IBD due to an inflammation-driven blockade as outlined above. There are other potential downsides associated with oral iron therapy. Oral iron increases the severity of experimental colitis and impacts the intestinal microbiome. The former is also ascribed to redox reactions which lead to the production of reactive oxygen species and mediate intestinal damage in rodents. In a murine colitis model an increased prevalence of intestinal adenomas was observed after prolonged treatment with oral but not parenteral iron. However, the important question remains what the impact of oral iron

![Figure 2](image-url)
on mucosal inflammation is in patients with IBD. From two randomized controlled trials a potential effect of iron supplementation on clinical disease activity could not be delineated, although the studies were not adequately powered to answer this question.56,57 Also the effect of oral iron on colorectal carcinoma in humans remains controversial and data on patients with IBD are missing.58–61

Data from eight clinical studies on the experience of IV iron therapy for IDA in IBD comprising a total of 719 patients showed that overall intravenous iron treated patients had higher response rates compared to patients treated with oral iron (Table 4).5,56,57,62–66 Additionally, it was found that treatment discontinuation due to adverse events was lower in patients treated with IV iron compared to patients treated with oral iron.67 Thus, IV iron is more effective and better tolerated than oral iron and is to be considered in patients with severe anemia (Hb <10.0 g/dL), with intolerance or inadequate response to oral iron and/or those with active IBD. Intravenous iron administration is the route of choice when simultaneous treatment with erythropoiesis stimulating agents (ESA) is considered.6

There has been much debate on whether low or high dose intravenous iron is more efficient in rapidly replenishing iron stores. Gisbert et al. reported a response rate in IBD patients of 77% with iron sucrose 2 × 200 mg/week,5 whereas Kulnigg et al. published an identical response rate of 77% in IBD patients using ferric carboxymaltose at a maximum dose of 1000 mg iron per infusion at 1-week intervals.56 These studies were comparable in terms of Hb concentrations at baseline being <10 g/dL and response being defined as an increase in Hb of ≥ 2 g/dL. However, the duration of the iron sucrose study was 26 weeks as compared to only 12 weeks in the ferric carboxymaltose trial.

More recently, the superiority of higher intravenous iron doses was shown in a comparative clinical trial of the efficacy and safety of standardized ferric carboxymaltose doses with respect to individually calculated iron sucrose doses.68 After 12 weeks ferric carboxymaltose was superior with regard to response rate, defined as an increase in Hb concentrations of ≥2 g/dL (66.1% versus 54.1%), proportion of non-anemic patients (72.8% versus 61.8%) and full adherence to the treatment regimen (92.5% vs. 79.1%), whereas there was no difference in treatment-related adverse events (13.9% vs. 11.3%). However, skin and subcutaneous tissue disorders such as rash, dermatitis, and pruritus that were related to the study drug occurred more frequently in the ferric carboxymaltose group than in the iron sucrose group (3.7% vs. 0.8%). Mean serum phosphate levels decreased from baseline to week 2 in the ferric carboxymaltose group and hypophosphatemia developed in 2.5% of patients in the ferric carboxymaltose group. The mechanism of the decrease in serum phosphate levels seen with ferric carboxymaltose is unknown. Infusion site reactions were observed more frequently in the iron sucrose group than in the ferric carboxymaltose group (2.5% vs. 0.4%) possibly because of the alkaline pH of the preparation and the higher number of infusions in the iron sucrose group.

The optimal target range for iron substitution has not been studied specifically. Iron homeostasis is regulated at intake and the bone marrow requires 20–30 mg/day for erythropoiesis, a demand which may increase to 50 mg/day in severe anemia. Iron supplementation for erythropoiesis is optimal at

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Summary of main characteristics and comparisons between current and new generation IV iron preparations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Low Mw iron dextran (Comipar®)</td>
</tr>
<tr>
<td>Manufacturer</td>
<td>Pharmacosmos</td>
</tr>
<tr>
<td>Carbohydrate molecule</td>
<td>Dextran (branched polysaccharides)</td>
</tr>
<tr>
<td>Maximum single dose</td>
<td>20 mg/kg</td>
</tr>
<tr>
<td>Single dose limit</td>
<td></td>
</tr>
<tr>
<td>Infusion within 1 h</td>
<td></td>
</tr>
<tr>
<td>Test dose required</td>
<td>Yes</td>
</tr>
<tr>
<td>Infusion concentration (mg/ml)</td>
<td>50</td>
</tr>
<tr>
<td>Vial volume (ml)</td>
<td>2</td>
</tr>
<tr>
<td>a There are data from a total of 570 infusions of 1 g of low Mw iron dextran in 250 ml normal saline over 1 h without premedication as standard practice.75</td>
<td></td>
</tr>
</tbody>
</table>
Table 4  Characteristics of the clinical trials involving IBD patients that compared IV iron administration with oral iron or no intervention included in this review.

<table>
<thead>
<tr>
<th>Study year (ref)</th>
<th>n</th>
<th>Study design</th>
<th>Compound</th>
<th>Baseline Hb (g/dL)</th>
<th>Total dose, mg (schedule)</th>
<th>Duration (weeks)</th>
<th>Response</th>
<th>DCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gasche et al., 2001</td>
<td>103</td>
<td>Multicenter, open-label</td>
<td>Iron sucrose</td>
<td>≤ 10.5</td>
<td>1200 mg (6 × 200 mg)</td>
<td>4</td>
<td>65%</td>
<td>0%</td>
</tr>
<tr>
<td>Bodemar et al., 2004</td>
<td>59</td>
<td>Retrospective</td>
<td>Iron sucrose</td>
<td>&lt; 12</td>
<td>Mean 1400 mg</td>
<td>8</td>
<td>60%</td>
<td>0%</td>
</tr>
<tr>
<td>Schröder et al., 2005</td>
<td>46</td>
<td>Multicenter Randomized</td>
<td>Iron sucrose (22)</td>
<td>&lt; 10.5 ♂</td>
<td>Mean 1418 mg</td>
<td>6</td>
<td>55%</td>
<td>4.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open-label</td>
<td>Ferrous sulfate (24)</td>
<td>&lt; 11 ♀</td>
<td>Mean 5600 mg (100–200 mg/day)</td>
<td>12</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>García-López et al., 2006</td>
<td>70</td>
<td>Single center</td>
<td>Iron sucrose</td>
<td>&lt; 10.5 a</td>
<td>Mean 920 mg (200–1800 mg)</td>
<td>Mean 5 (1–9)</td>
<td>67%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospective</td>
<td>Carboxymaltose (200 mg/1–2 infusions of 500–1000 mg)</td>
<td></td>
<td>16800 mg (200 mg/day)</td>
<td>12</td>
<td>77%</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Observational</td>
<td>Ferrous sulfate (24)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kulnigg et al., 2008</td>
<td>200</td>
<td>Multicenter Randomized</td>
<td>Ferric</td>
<td>≤ 10</td>
<td>1000–1500 mg (1–2 times a week)</td>
<td>12</td>
<td>77%</td>
<td>1.5%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Open-label</td>
<td>Carboxymaltose (137)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ferrous sulfate (63)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lindgren et al., 2009</td>
<td>91</td>
<td>Multicentre Randomized</td>
<td>Iron sucrose (45)</td>
<td>&lt; 11.5</td>
<td>Mean 1700 mg (200 mg/1–2 weeks)</td>
<td>20</td>
<td>66%</td>
<td>7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Investigator-blinded</td>
<td>Ferrous sulfate (46)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gisbert et al., 2009</td>
<td>100</td>
<td>Multicenter, open-label</td>
<td>Iron sucrose (22)</td>
<td>&lt; 10</td>
<td>Not reported (2 × 200 mg/week if Hb &lt;10)</td>
<td>26</td>
<td>77%</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ferrous sulfate (78)</td>
<td>&gt; 10</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koutroubakis et al., 2010</td>
<td>50</td>
<td>Single center</td>
<td>Low molecular weight Iron dextran</td>
<td>&lt; 10 ♀ a</td>
<td>800–1600 mg (106 mg/day)</td>
<td>4</td>
<td>23%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Prospective</td>
<td></td>
<td>&lt; 11 ♂ a</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
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<td>Observational</td>
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Response: Hb ≥ 2 g/dL or normal Hb; DCT: discontinuation due to serious adverse events.

a Also those patients with no response or intolerance to oral iron, or with clinical need of quick recovery from anemia.
TfS of 30–40% and serum ferritin of 400–500 μg/L and this is particularly important for patients already being treated for IDA. Over-supplementation could theoretically result in iron deposition in parenchymatous organs. However, data from patients with thalassemia suggest that this risk appears negligible. An iron overload of the macrophages in the reticulo-endothelial system may induce an over-expression of ferroportin which may allow, via bypassing the hepcidin block in ACD, an iron flow to the bone marrow. This could explain the superiority of high intravenous iron supplementation in IBD. In addition macrophage iron loading may inhibit pro-inflammatory immune effector pathways. Nevertheless, iron therapy is not recommended in sepsis because it may potentially worsen the disease.

The aim of iron therapy is the normalization of iron stores and ensuring the increase of Hb concentrations into the normal range (Fig. 1). However, neither the optimal Hb concentration which is to be achieved nor the preferred approach on how to calculate the necessary iron dose has been studied in detail in IBD. The Ganzoni formula captures total body iron deficit in mg = (body weight in kg × [target hemoglobin – actual hemoglobin in g/dL] × 0.24) + 500. The formula is based on a hemoglobin target concentration of 15 g/dL, a hemoglobin iron concentration of 0.37%, a blood volume making 7% of body weight and a demand of iron stores of 500 mg. More recently, an alternative dosing scheme also based on hemoglobin concentration and body weight has been presented for dosing of ferric carboxymaltose. For a baseline hemoglobin of ≥ 10 g/dL dosing was 1.0 g for patients with a body weight less than 70 kg and 1.5 g for patients ≥ 70 kg. The corresponding total doses for serum hemoglobin ≤ 10 mg/dL were 1.5 g and 2.0 g. Mathematical models might be utilized in the future not only to identify causes of anemia in patients with IBD, but also to estimate the total iron dose required to replenish deficient stores.

To date treatment should strive for ferritin concentrations of >100 μg/L. However, after intravenous iron treatment reliable ferritin concentrations reflecting iron stores should be measured as early as 8 weeks after therapy. An increase in Hb is associated with improved quality of life scores and better cognitive functions in patients with IBD. These changes are independent of disease activity.

IDA is a recurrent problem, which requires continuous attention and follow-up by the physician. A retrospective analysis of 88 patients with IBD treated with IV iron ± erythropoietin revealed the frequent recurrence of anemia within only months after supplementation. Thus, regular controls, e.g. at 12 week intervals are advocated and retreatment initiated as soon as Hb concentrations or iron parameters are below the levels indicated above. The existence of ID in asymptomatic patients with IBD should always spur the suspicion of a physician on subclinical inflammatory activity as the discrepancy between clinical symptoms and endoscopic lesions is a well known phenomenon.

7. New entries of iron supplementation

One of the putative concerns with IV iron administration has been the issue of free (catalytic) iron reactions occurring during the transportation of iron in the body. Recently, IV iron formulations have been introduced in which this potential problem is minimized due to a strongly bound iron carbohydrate complex. In both iron caboxyximaltose and ferumoxytol an iron core is wrapped in a carbohydrate shell that shields the activity of ferric iron to the plasma (Fig. 3a). Only 2–3% of the ferric iron in the administered dose passes directly to transferrin in the plasma, whereas the whole complex is taken up by macrophages in the reticulo-endothelial system (RES). The iron complex is subsequently degraded and iron transferred to transferrin with a negligible free iron reaction. A similar mechanism occurs for iron isomaltoside 1000 which consists of a matrix with interchanging iron and carbohydrate molecules (Fig. 3b).

These novel structures of the new IV iron formulations not only reduce this risk of free iron reactions, but are also of lower immunogenicity which allows treatment initiation without administering a test dose. Thus, IV iron is becoming available in safer formulations that are administered in a more time-efficient fashion as a high dose infusion (Table 3).

Figure 3 The iron core is: (a) wrapped in a carbohydrate shell (iron carboxymaltose and ferumoxytol) or alternatively, (b) enmeshed in a matrix with interchanging iron and carbohydrate molecules (iron isomaltoside 1000). The strongly bound iron in the new preparations allows only a low level of free iron to circulate in the blood, hence improving safety.
8. Total dose infusion of IV iron

Older generations of IV iron preparations required multiple visits for full iron repletion (iron sucrose, iron gluconate) or a prolonged duration of administration (4–6 h for HMWID, LMWID). The safety and efficacy of HMWID was retrospectively evaluated in 70 pediatric patients with IBD who received 119 total dose infusions. The average increase in Hb concentration was 2.9 g/dL, but the risk of hypersensitivity reactions should urge clinicians not to use HMWID anymore. Koutroubakis et al. reported total dose infusions with LMWID in 50 patients with IBD with a 10% rate of adverse events, most of them after the administration of the test dose. Auerbach et al. published data on a total of 570 infusions of 1 g of LMWID in 250 mL normal saline over a median time of 63 min [interquartile range: 60–66 min] without premedication, but for which a test dose is still required. The most common diagnoses were heavy uterine bleeding among women (43.5%) and gastrointestinal bleeding among men (33.3%). A total of 41 adverse events were reported in 22 patients (5.6%), with six patients requiring a decreased rate or temporary interruption of the infusion. There were no anaphylactoid reactions and no serious adverse events. Therefore, in countries where newer IV iron formulations are not available or the cost of the new formulations is a problem, the total dose infusion of LMWID may be still a choice for treating IBD associated IDA.

The new generation of IV iron preparations allows for administration of much higher single doses up to 20 mg/kg body weight with iron isomaltoside 1000 (max: 2000 mg) or ferric carboxymaltose (max: 1000 mg), in a short time (15–60 min; Table 3). Ferumoxytol can be administered at doses of 510 mg in less than 1 min. However, in the current package insert, the recent bolded recommendation for a 30 min observation time, as well as the need for a second visit to complete dosing, eliminates some of the benefit of the short infusion time. Additionally, ferumoxytol might be problematic in patients with IBD because it can interfere with MRI signals due to the paramagnetic nature of its iron core.

The omission of a test dose further improves the convenience of these new IV iron preparations and lowers costs in terms of the time spent at the hospital, including treatment and waiting time. Furthermore, travel for continuous treatments can be reduced in addition to a reduction of nursing and medical time as well reduced cost of administration. For a total iron dose of 1000 mg, ferric carboxymaltose could provide significant saving when compared with iron sucrose in IBD and surgery. Cost effectiveness of total dose infusion has been shown in patients with chronic kidney disease by calculated saved costs of around $300 per patient per year. This suggests that total dose infusion is a valuable tool for the efficient and cost effective treatment of patients with IDA in various therapeutic areas.

9. Safety of IV iron

IV iron is generally well tolerated. In patients with renal disorders (chronic kidney disease, dialysis patients and high risk groups such as transplant patients) IV iron has been used safely for the treatment of anemia for many years and has been demonstrated not to increase mortality or affect disease progression. IV iron is becoming increasingly established for the treatment of ID and IDA in other medical disciplines, i.e. gastroenterology, hematology, cardiology, oncology, gynecology, and for pre- and postoperative use.

The acute safety differences among IV iron products are small when given at the recommended doses. Moreover, safety of IV iron is better compared to that associated with red cell transfusions. According to data from FDA (2001–2003; 30 × 10^6 doses) the incidence of life-threatening adverse drug events (ADEs), including deaths, associated with the use of IV iron is much lower than that associated with the use of allogenic blood transfusion.

When HMWID is avoided, the incidence of serious adverse events with the newer formulations is <1:200,000, thus far less than would be expected in any series where oral iron would be given to patients with IBD. HMWID in contrast to low molecular weight iron dextran LMWID has an increased rate of severe side effects and deaths due to anaphylactic reactions and this was the clinical safety rationale for development of new IV iron preparations. It is believed that the immunogenicity of the carbohydrate per se increases the risk of anaphylactoid or anaphylactic reactions hence a test dose is required, which has been studied carefully in patients with renal disease.

The newer IV iron preparations demonstrate potentially much lower immunogenic activity than the old ones. Therefore they are approved without requirement for a test dose, indicating a minimal risk of anaphylactoid or anaphylactic reactions. The construction of the newer IV iron preparations allows for a slow release of iron which minimizes the risk of free iron toxicity even in high dose IV iron preparations, hence minimizing the risk for oxidative stress and damage caused by lipid peroxidation to e.g. the liver. Experimental data from Jahn et al. demonstrating free iron levels, noted that there were low levels for all iron preparations (<0.3%) using unbuffered saline. Interestingly, when the experiment was performed using buffered 0.9% NaCl solution at pH 7.4, the free iron content was below the detection limit of the method (<0.002%) for iron isomaltoside 1000, iron carboxymaltose and ferumoxytol. Switching to standard saline, which does not contain a buffer led to a 100 fold increase (<0.002% to 0.262%) in the content of free iron in iron carboxymaltose. Hence the dialyzable iron in iron carboxymaltose is sensitive to pH. The relevance of this is unclear but it should be noted that dilutions of IV iron formulations for drip infusion are prepared in non buffered physiological saline solutions. Reassuringly however for the clinician administration of 1000 mg iron dose represents the release of a maximum of 2.62 mg of free iron over 24 h, which amounts to only 40% of the capacity of transferring to bound iron, such that the probability of increasing free iron in the blood seems low. Nevertheless, more studies on long-term safety of the newer IV iron preparations are warranted and data are needed to examine whether there is a variation in tissue iron deposition and toxicity. IV iron has been used for more than twenty years by nephrologists in chronic kidney disease and is a well established entity in patient care for chronically ill patients among nephrologists. Thus, the potential concern of iron overload due to IV iron therapy appears hypothetical.
In patients suffering from chronic kidney disease the beneficial role of IV iron is confirmed by being associated with a lower rate in morbidity, hospitalization, and mortality compared to patients not receiving IV iron. Perioperative infusion of IV iron has been demonstrated to significantly lower the need for transfusions and to lower the postoperative rate of infections. 84

10. Summary

Iron deficiency anemia is a frequent complication of IBD which impressively adds to its morbidity. Awareness of gastroenterologists needs to be increasingly directed to the diagnosis and treatment of iron deficiency in these patients. With the new generation of IV iron compounds a safe and highly efficient treatment has become available and should help to overcome the reservation of gastroenterologists to replenish deficient iron stores in patients with IBD according to existent guidelines. Improved tolerability and patient convenience by rapidly restoring depleted iron status of patients with IBD has been demonstrated.

Conflict of interest

The authors received a speakers honorarium from Pharmacosmos for giving lectures at a satellite symposium “State-of-the-Iron” during UEGW 2010 in Barcelona.

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References

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