Management of iron deficiency anemia in inflammatory bowel disease – a practical approach

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Abstract

Although anemia is the most common systemic manifestation of inflammatory bowel disease (IBD), among the broad spectrum of extraintestinal disease complications encountered in IBD, including arthritis and osteopathy, it has generally received little consideration. However, not only in terms of frequency, but also with regard to its potential effect on hospitalization rates and on the quality of life and work, anemia is indeed a significant and costly complication of IBD. Anemia is multifactorial in nature, the most prevalent etiological forms being iron deficiency anemia (IDA) and anemia of chronic disease. In a condition associated with inflammation, such as IBD, the determination of iron status using common biochemical parameters alone is inadequate. A more accurate assessment may be attained using new iron indices including reticulocyte hemoglobin content, percentage of hypochromic red cells or zinc protoporphyrin. While oral iron supplementation has traditionally been a mainstay of IDA treatment, it has also been linked to extensive gastrointestinal side effects and possible disease exacerbation. However, many physicians are still reluctant to administer iron intravenously, despite the wide availability of a variety of new IV preparations with improved safety profiles, and despite the recommendations of international expert guidelines. This article discusses improved diagnostic and therapeutic strategies based on new clinical insights into the regulation of iron homeostasis.

Keywords

Inflammatory bowel disease, extraintestinal manifestations, anemia, iron deficiency, iron supplementation

Ann Gastroenterol 2012; 26 (1): 1-10

Introduction

Iron deficiency occurs in about 60-80% of patients with inflammatory bowel disease (IBD), and anemia manifests in approximately one-third of patients. Anemia is thus by far the most common extraintestinal complication of IBD [1]. In a recent review by Gisbert and Gomollón, study data showed the prevalence of anemia in patients with IBD to range from 16-74%, with a mean value of 16% in outpatients and 68% in hospitalized patients [1]. Goodhand et al [2] demonstrated in a more recently-published prospective trial that anemia and iron deficiency anemia (IDA) are particularly prevalent in children, the incidence of anemia being 70% in children, 42% in adolescents, and 40% in adults. Iron deficiency was also found to occur more commonly in children (88%) and adolescents (83%) than in adults (55%). This high prevalence of IDA in children was confirmed by a more recently published retrospective cohort study of Wiskin et al in which at diagnosis 75% of children were anemic and 90% (Crohn's disease, CD) to 95% (ulcerative colitis, UC) were iron deficient. At follow up two years later 70% of children with CD and 65% of children with UC were iron deficient [3].

Typical symptoms of a manifest iron deficiency with secondary microcytic, hypochromic anemia include reduced performance, fatigue, headache, dizziness and tachycardia, as well as exertional and even resting dyspnea. In addition, latent iron deficiency may be responsible for “non-hematological” symptoms such as hair loss, paresthesia of the hands and feet and reduction in cognitive function, and also has a significant association with “restless legs syndrome”. This leads to considerable deterioration in the patient’s quality of life, increased time lost at work and more frequent hospitalization [4].
Pathophysiology of iron deficiency anemia in IBD

The cause of anemia in patients with IBD is multifactorial (Table 1). The two most frequent etiological forms by far are IDA, resulting from iron deficiency secondary to blood loss through the ulcerations of the intestinal mucosa, reduced iron absorption and reduced intake [4], and anemia of chronic disease (ACD), described for the first time by Cartwright in 1946 [5]. ACD is characterized by normal or reduced mean corpuscular volume (MCV), reduced serum iron, reduced total iron binding capacity (TIBC), normal to elevated serum ferritin level, and reticuloendothelial system (RES) stores that are elevated relative to total body iron. While Vitamin B12-folate deficiency and drug-induced anemia (sulfasalazine, thiopurines, methotrexate, calcineurin inhibitors) are less widespread, these possibilities should also be considered.

The human body stores approximately 3-4 g (40-50 mg/kg) of iron, while desquamation of the epithelial cells of the skin, the gastrointestinal tract, the bile ducts and the urinary tract, and blood loss during menstruation account for daily losses of around 1-2 mg. Mammalian iron homeostasis is controlled exclusively by means of iron absorption from the duodenum (and to a lesser extent in the proximal jejunum) in both the healthy and the inflamed state, and is tightly regulated by hepcidin (Fig. 1).

Hepcidin, an antimicrobially-acting acute-phase protein of about 25 amino acids in size, binds to the basolateral transporter, ferroportin 1, triggering its tyrosine phosphorylation and internalization by binding JAK2, which leads to ubiquitin-mediated degradation in lysosomes [6,7]. The enterocyte iron content increases in response to the removal of ferroportin 1 from the plasma membrane, causing a secondary (but physiologically less relevant) reduction in the expression of DcytB and DMT1. Moreover, hepcidin effects the suppression of iron release from macrophages and monocytes.

During infection and inflammation, the upregulation of hepcidin gene expression occurs as a result of the action of proinflammatory cytokines - mainly interleukin (IL)-6, involving JAK-dependent activation of STAT 3. This elevation shows an inverse correlation with body iron stores [8] (Fig. 1).

Diagnostic work-up of iron deficiency in IBD

Anemia is defined by the WHO as a decline in blood hemoglobin to a concentration of <12 g/dL (120 g/L) in women and <13 g/dL (130 g/L) in men, parameters which are equally applicable to patients with IBD. When anemia is assessed on the basis of hemoglobin levels, the influence of a range of other factors must, however, be taken into account: pregnancy, altitude, cigarette smoking, and possibly ethnicity [9]. The WHO has therefore additionally issued respective international minimum levels for hemoglobin and hematocrit (Table 2).

The standard parameters of iron deficiency, low MCV and low mean corpuscular hemoglobin (MCH) are generally reliable. However, iron deficiency as the cause of anemia cannot be ruled out on the grounds of a normal MCV, since up to 40% of "pure" IDA cases are normocytic (e.g. in IBD patients treated with azathioprine or 6-MP). Conversely, low MCV does not necessarily indicate ID, as the presence of ACD can cause it to be normal or low [4,10]. A substantially more accurate IDA diagnosis can be attained by the additional determination of iron metabolism parameters [4]. In principle, all components of the body's iron metabolism can be conveniently monitored using routine laboratory methods:

- Iron stores: serum ferritin
- Iron transport: transferrin saturation
- Iron utilization: erythropoiesis: i.e. proportion of hypochromic erythrocytes or reticulocytes

Serum iron concentrations are governed by a circadian rhythm and can be low even in cases of anemia of chronic
Management of iron deficiency anemia in IBD

Reticulocytes

Reticulocytes are those immature erythrocytes still containing sufficient RNA as to be microscopically detectable using specific alkaline stains. This blood count parameter (%) is obtained by flow cytometry and is available in all larger laboratories at a reasonable cost.

In chronic anemias that have reached a steady state, the relative reticulocyte count correlates inversely, though non-linearly, with the shortening of the erythrocyte lifespan. The absolute reticulocyte count, on the other hand, is a gauge for effective erythrocyte production by the bone marrow.

The reticulocyte production index (RPI) describes the relative reticulocyte count (RTC, in %) corrected to the severity of the anemia (patient’s hematocrit [HCT-P] in relation to ideal hematocrit [HCT-N = 0.45] and reticulocyte maturation time [RMT]):

$\text{RPI} = \frac{(\text{RTC} \times \text{HCT-P})}{(\text{HCT-N} \times 0.45 \times \text{RMT})}$

The RPI thus represents the increase or decrease in erythrocyte production as a factor of the normal value 11.

Serum ferritin

Serum ferritin is an indicator of the storage iron content of the RES, and is therefore employed to detect malfunction in cellular iron storage. The reference range is 15-100 μg/L for women and 30-200 μg/L for men; a serum ferritin concentration of 100 μg/L represents about 1000 mg of stored iron. Reduced concentrations are a sign of iron deficiency, and a serum ferritin concentration <15 μg/L is considered...
an indication of absolute iron deficiency. However, because both ferritin and transferrin belong to the family of acute-phase proteins, these reference ranges cannot be applied to patients with active IBD [4,12]. Recent guidelines therefore recommend that, in the presence of inflammation (i.e. CRP >5), sensitivity and specificity can be improved by using a cutoff value ≤ 100 µg/L [12].

Transferrin saturation

Transferrin saturation (TfS) is a measure for the iron load of circulating transferrin. It says nothing, however, about the condition of the iron stores, providing only an indirect indication of the extent of iron utilization. Under physiological conditions, 16-45% of transferrin molecules in plasma are “loaded” with iron (3-4 mol of iron per mol of transferrin), and a saturation of <16% is considered to represent a suboptimum iron supply for the erythropoietic process. While reduced transferrin saturation (<20%) is accredited with a relatively high sensitivity (90%) for recognizing iron deficiency states, its specificity is poor (40-50%). Since measurements of both serum iron and serum transferrin are subject to quite significant circadian effects, blood samples should always be obtained at the same time of day and repeated frequently. Serum transferrin levels are increased in patients taking oral contraceptive steroids, but reduced in the presence of inflammation (negative APP), meaning that, in patients with acute or chronic inflammatory disorders, TfS may be reduced despite normal iron stores [4].

Soluble transferrin receptors

An up-regulation of the number of soluble transferring receptors (sTfR) on the cellular membranes continuously moving into the plasma is consistent to all cases of functional iron deficiency, its extent being entirely independent of chronic inflammation or hepatic damage. Thus, the determination of sTfR has been reported to be a reliable indicator of iron deficiency [13].

However, sTfR concentrations are also increased in every expansion of erythropoiesis (i.e. hemolytic anemia, thalassemia or polycythemia) and reduced in aplastic anemia and other conditions with hypoproliferative erythropoiesis (e.g. renal anemia). This assay has been found to have a specificity for IDA of 84%, but a PPV of only 54%, and has been demonstrated to be less accurate than serum ferritin [14]. Likewise, the combination of ferritin and sTfR (sTfR/log ferritin ratio) proposed by Punnonen [15,16] has not proved effective as a more accurate means of differentiation between IDA and ACD [17,18]. These data are in contrast to a recently published case-control study in anemiac IBD demonstrating that a sTfR – Index >1.4 had a 91% sensitivity and 92% for the diagnosis of IDA [19,20]. Disadvantageous for the routine diagnostic use of the TIR-F index are its lack of uniform reference range (the reference ranges of the individual components are assay-dependent) and the relatively high costs. It may be hypothesized, that the combination of hematologic markers such as reticulocyte hemoglobin content, which decreases with iron deficiency, and R/F ratio may allow for a more precise classification of anemias [21].

Hypochromic erythrocytes/reticulocytes

Recent research by Thomas et al has confirmed cytometry of the reticulocyte hemoglobin content (CHr) and the percentage of hypochromic red cells (%HYPO) to have a high predictive value in the differential diagnosis of IDA, even when inflammation and ACD are present [15,17]. While a reduction in %HYPO (mean lifetime of 120 days) denotes a longer-term deficiency in iron supply, reduced CHr (mean lifetime of 48 h) is an indicator of current iron deficiency, providing an accurate measurement of bioavailable iron over the previous 3-4 days (Table 3). In hemodialysis patients, CHr <29 pg has been demonstrated to be a more accurate measure of functional iron deficiency than the combined use of ferritin and TfS. Furthermore, CHr measurement may serve to predict the response to intravenous (IV) iron therapy within 2-4 days after onset [15,17]. However, there are no data available from IBD patients.

Zinc protoporphyrin

Zinc protoporphyrin (ZPP) was pinpointed by Dagg and colleagues as early as 1966 as a potential indicator of ID [22]. In the terminal reaction in heme synthesis – catalyzed by the mitochondrial enzyme ferrochelatase - iron is chelated by protoporphyrin, while the metal-binding site on ferrochelatase may be claimed by iron or zinc [23]. A reduction in iron supply for erythropoiesis to a suboptimal level results in the production of ZPP instead of heme, with zinc, instead of iron, being incorporated into protoporphyrin IX. Thus, ZPP levels are a direct marker of iron status in the bone marrow during erythropoiesis. ZPP production is entirely unaffected by ACD or other chronic inflammation, and is therefore an effective indicator of ID even in the presence of inflammation [23,24]. The onset of iron-deficient erythropoiesis triggers continuously increasing ZPP concentrations. Concentrations <40 µmol/mol heme are considered normal. Values of 40-80 µmol/mol heme represent latent iron deficiency (hemoglobin normal); >80 µmol/mol heme are associated with manifest iron deficiency. In severe cases, values up to 1000 µmol/mol heme have been reported [23,24]. Thus, ZPP determination not only detects iron-deficient erythropoiesis but can also quantify it. Theoretically, as zinc deficiency is also not uncommon in inflammatory disorders [25], ZPP values may be false negative in zinc deficiency patients [4].

The choice of laboratory parameter depends on both the clinical question posed and the availability of the respective test. However, the first-line parameter for assessing iron metabolism in routine clinical practice is serum ferritin. Due to its correlation with iron store repletion levels, this is the most sensitive gauge of iron metabolism and, in contrast to the other
laboratory parameters, can expose iron storage deficiencies. When interpreting ferritin concentrations, however, it must be born in mind that inflammatory or malignant disease, liver disease and pregnancy may lead to false normal or elevated ferritin concentrations, and thus disguise an existing iron deficiency. A diagnostic panel consisting of ferritin, hemoglobin and CRP is in most cases adequate to confirm iron deficiency as the cause of anemia with acceptable diagnostic certainty. In unclear cases, these findings can be supplemented, depending on availability, with sTfR, ZPP, %HYPO and CHr. While these parameters, in contrast to ferritin, detect iron deficiency only at or beyond the stage of iron-deficient erythropoiesis, they are not impacted by inflammatory or malignant disease.

**Treatment of iron deficiency anemia in IBD**

Iron supplementation should be administered in all cases of manifest anemia [12]. Cases of iron deficiency without manifest anemia require an individualized approach according to clinical symptoms. In these cases, the timing and type of therapy is determined according to symptoms, etiology, degree of severity and dynamics of the hemoglobin decrease, and the comorbidities and risks of therapy [4]. Iron supplementation can be administered orally or intravenously.

**Oral iron administration**

Oral iron supplementation has been the therapy of choice for many years. Despite recent recommendations of international expert guidelines, the use of IV iron preparations remains the subject of safety worries and is therefore still widely considered a last resort [12].

In IBD patients, iron(II) or iron(III) compounds may be administered orally in the absence of absolute indications for IV therapy (see below), and in IBD patients with mild anemia (Hb >10 g/dL) and inactive disease oral iron replacement can be used. This approach is supported by an the recently published study of Lomer et al [26] and our own data [27], which showed, that intestinal iron absorption is normal in quiescent or mildly active IBD patients.

However, as more than 90% of ingested iron remains unabsorbed, oral iron supplementation is associated with the frequent occurrence of gastrointestinal adverse effects, such as nausea, flatulence, diarrhea and gastric erosion. Furthermore, a potential for the exacerbation of IBD through the generation of reactive oxygen species (Fenton reaction) by non-absorbed iron has been revealed in both animal and human studies [28-30]. Upon initiation of oral iron supplementation, the patient's response, tolerance and adherence should therefore be monitored. Patients showing insufficient response (Hb increase <2 g/dL within 4 weeks) or intolerance to oral iron, as well those with severe IDA (≤10 g/dL) and active disease (CRP >5 mg/L), should receive IV iron as first-line therapy [12].

**Intravenous iron administration**

IV iron therapy is recommended for iron-deficient patients who display intolerance or an inadequate response to oral preparations (i.e. insufficient increase in serum iron parameters within the first two weeks of treatment), severely anemic patients (Hb level <10 g/dL), those who have pronounced disease activity, and those undergoing treatment with erythropoiesis stimulating agents (ESAs) [12]. However, although the clinical efficacy and good safety

<table>
<thead>
<tr>
<th>Laboratory Measures</th>
<th>Normal</th>
<th>IDA</th>
<th>ACD</th>
<th>IDA/ACD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone marrow iron</td>
<td>2-3</td>
<td>0-1</td>
<td>2</td>
<td>1-2</td>
</tr>
<tr>
<td>Serum iron</td>
<td>40-165 µg/L</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Mean corpuscular volume</td>
<td>80-96 fl</td>
<td>↓</td>
<td>↓ or n</td>
<td>↓ or n</td>
</tr>
<tr>
<td>Serum ferritin</td>
<td>16-350 µg/L</td>
<td>↓</td>
<td>↑</td>
<td>↑ or n</td>
</tr>
<tr>
<td>Transferrin</td>
<td>↑</td>
<td>↑</td>
<td>↓ or n</td>
<td>↓</td>
</tr>
<tr>
<td>Transferrin saturation</td>
<td>20-50%</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>*sTfR</td>
<td>0.8-2.2 mg/l</td>
<td>↑</td>
<td>n or ↓</td>
<td>↑ or n</td>
</tr>
<tr>
<td>*sTfR-F index</td>
<td>high (&gt;2)</td>
<td>high (&gt;2)</td>
<td>low (&lt;1)</td>
<td>high (&gt;2)</td>
</tr>
<tr>
<td>CHr</td>
<td>≥ 29 pg</td>
<td>↓</td>
<td>n or ↓</td>
<td>↓</td>
</tr>
<tr>
<td>PHRC</td>
<td>1-5%</td>
<td>&gt;5%</td>
<td>&lt;5%</td>
<td>≥5%</td>
</tr>
<tr>
<td>*Zinc protoporphyrin</td>
<td>&lt; 40 (µmol/mol heme)</td>
<td>&gt;80</td>
<td>≥80</td>
<td>≥80</td>
</tr>
<tr>
<td>C-reactive protein</td>
<td>&lt; 5 mg/L</td>
<td>n</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

*values vary according to the different assays
IDA, iron deficiency anemia; ACD, anemia of chronic disease; CHr, Reticulocyte hemoglobin content; PHRC, Percentage of hypochrome erythrocytes; sTfR, Serum transferrin receptor; sTfR-F, Soluble transferrin receptor/log ferritin

**Table 3 Laboratory findings in IDA, ACD and in mixed IDA/ACD**

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profile of IV iron have been clearly demonstrated in a number of observational and controlled studies in UC and CD patients, many gastroenterologists are still apparently reluctant to administer iron intravenously, for fear of hypersensitivity reactions [31].

There are now six IV iron preparations available which have a good safety record in other diseases (Table 4). Over the last decade, iron sucrose (IS) has become standard of care in IBD, due to its proven efficacy, wide availability and excellent safety record [32-38]. However, since a large number and frequency of applications is required (maximum dose 600 mg per week) and administration is relatively time-consuming (3.5 h for a 500 mg dose), the practicality of IS for the achievement of high level iron repletion is limited.

A new option for iron supplementation is the recently-approved, novel generation of so-called Type I IV iron preparations, which can be applied in high single doses (so-called “total dose infusions, TDI”). As yet, data in IBD patients are available only for low molecular weight (LMW) iron dextran preparations and ferric carboxymaltose. The efficacy and safety of LMW - iron dextran preparations (e.g. Cosmofer®) in IBD patients with IDA have been studied both in children [39] and in adults [40,41], demonstrating a significant hematopoietic response. However, iron dextrans have been associated with the occurrence of IgE-mediated anaphylactic reactions, reported in these studies to be 2-6% in spite of a successful test infusion [40,41]. LMW - iron dextran preparations allow the total iron dose to be given in only 1-2 Infusions. However, administration of LMW-iron dextran at this dose level is time-consuming, taking some 4-6 h. This not only inconvenient, but also results in loss of patient productivity.

**Ferric carboxymaltose** (Ferinject*), is a stable, macromolecular (150 kDalton) ferric hydroxide carboxymaltose complex which can be administered at a dose of up to 1000 mg in only 15 min. To date, safety and efficacy data regarding the IV administration of ferric carboxymaltose (FCM) are available for over 3,500 patients with IDA resulting from chronic kidney disease [42,43], congestive heart failure [44,45], pregnancy, and postpartum [46,47]. In most of these trials, patients received FCM equivalent to an iron dose of ≤ 1000 mg (or 15 mg/kg in those weighing less than 66 kg) given as an infusion over ≤ 15 min, with subsequent weekly infusions. Two randomized studies have confirmed the superiority of this new formulation in IBD patients, the first of these [48] showing the drug to be efficacious and well-tolerated when compared with oral iron, and the second demonstrating the efficacy and safety of the drug compared to iron sucrose in a multinational, randomized study including more than 550 patients [49]. Ferric carboxymaltose was considerably more effective in correcting anemia than iron sucrose; more patients on ferric carboxymaltose showed hemoglobin values increased by ≥20 g/L, or achieved normalization of hemoglobin levels, than with IS. Moreover, since FCM required a mean of only 2.1 15-min infusions, as opposed to 5.8 infusions of 1 h duration in the iron sucrose group, it was also found to be

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**Table 4** Preparations available for intravenous iron supplementation (April 2012)

<table>
<thead>
<tr>
<th>Iron dextran (LMW)</th>
<th>Iron gluconate</th>
<th>Iron sucrose</th>
<th>Iron carboxymaltose</th>
<th>Ferumoxytol</th>
<th>Iron Isomaltoside</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>165 kD</td>
<td>37.5 kD</td>
<td>43.3 kD</td>
<td>150 kD</td>
<td>731 kD</td>
</tr>
<tr>
<td>Complex stability</td>
<td>High</td>
<td>Low</td>
<td>Moderate</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Test dose required</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Maximum approved dose</td>
<td>20 mg/kg BW</td>
<td>62.5 mg</td>
<td>200 mg*</td>
<td>1000 mg if patient weight &gt; 66 kg</td>
<td>510 mg</td>
</tr>
<tr>
<td>Maximum Infusion period</td>
<td>360 min</td>
<td>30 min</td>
<td>210 min</td>
<td>15 min</td>
<td>17 sec</td>
</tr>
<tr>
<td>Maximum single dose on injection</td>
<td>200 mg</td>
<td>62.5 mg</td>
<td>200 mg</td>
<td>500 mg</td>
<td>510 mg</td>
</tr>
<tr>
<td>Minimum Infusion period</td>
<td>2 min</td>
<td>10 min</td>
<td>10 min</td>
<td>Bolus</td>
<td>17 sec</td>
</tr>
<tr>
<td>Dose-related reactions</td>
<td>Hypotension, edema</td>
<td>Hypotension, edema</td>
<td>Hypotension, edema</td>
<td>None reported</td>
<td>None reported</td>
</tr>
<tr>
<td>Relative risk of severe side effects</td>
<td>Moderate</td>
<td>Low</td>
<td>Very low</td>
<td>None reported</td>
<td>Very low</td>
</tr>
<tr>
<td>Costs per 500 mg (€)**</td>
<td>84-86</td>
<td>52-56</td>
<td>105-110</td>
<td>170-175</td>
<td>170-175</td>
</tr>
</tbody>
</table>

*In most countries the dosage is fixed to 200 mg (label), in some countries 500 mg are approved
** in Germany August 2012
*** approved by the EMEA in April 2012, but not yet available
LMW, low molecular weight
considerably more convenient for patients [49].

While transient hypophosphatemia has been encountered in some individuals treated with ferric carboxymaltose (e.g., 2.5% of patients in the Evstatiev trial [49]), the potential consequences and clinical relevance of this phenomenon remain unclear. In early trials, unexplained differences in mortality rates between the treatment and control arms were observed [50].

**Ferumoxytol** (Feraheme®) is an iron polyglucose sorbitol carboxymethylether complex approved by the FDA in June 2009 as an injectable formulation for the treatment of IDA in patients with chronic kidney disease (CKD). This preparation allows rapid injection (<1 min) of up to 510 mg iron [51,52] and repeated administration at 3-8 day intervals. In the absence of published data regarding the administration of higher doses, however, several visits are required to complete dosing. This, together with the recommendation in the current package insert for a 60-min observation time, diminishes the advantages of the shorter infusion time [53].

It is important to note that, due to its superparamagnetic properties, ferumoxytol may alter MRI images for up to 3 months post administration [53]. Since MRI techniques play a significant role in diagnostic procedure in IBD patients [54], this must be considered an additional disadvantage at least in the IBD population [55]. To date, there are no data available for ferumoxytol in the context of IDA treatment in patients with IBD.

**Iron isomaltoside 1000** (Monofer®) is the newest IV iron product. As Monofer has a very low immunogenic potential and contains very little labile and free iron [56], a rapid high-dose infusion of doses exceeding 1000 mg may be administered, without the necessity for a test dose. Dose flexibility is thus optimized, so that full iron repletion may be achieved with a single infusion (one-dose iron repletion). Iron isomaltoside 1000 has been shown to be clinically well tolerated, safe and effective, and no anaphylactic or delayed allergic reactions have been reported. This new IV iron preparation would therefore appear to be a valuable alternative for the treatment of anemia in CKD [57]. However, as in the case of ferumoxytol, there are as yet no published data for IBD.

**Managing intravenous iron therapy**

The primary aims of iron supplementation therapy for IDA are to effect an increase in hemoglobin levels of >2 g/dL or achieve normal values within 4 weeks, to replenish iron stores (transferrin saturation >30%), to relieve symptoms of anemia, and to thereby enhance quality of life [4,12].

In current practice, the Ganzoni Formula (Iron deficit [mg] = body weight [kg] x (target Hb-actual Hb [g/dL] x 2.4) + stored iron (500 mg)) is used to calculate individual iron requirement. However, this formula is error-prone, inconvenient and inconsistently applied in clinical practice, and in fact underestimates iron requirements [48]. In a study comparing a novel fixed-dose regimen (Table 5) of ferric carboxymaltose (FERGIcor) with individually Ganzoni-calculated doses of IS in IBD patients with IDA, the novel fixed-dose regimen was shown to be superior in terms of both efficacy and safety profile (Fig. 2).

<table>
<thead>
<tr>
<th>Table 5 Total iron dose with the ferric carboxymaltose dose regimen [49]*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb [g/dL]</td>
</tr>
<tr>
<td>≥10</td>
</tr>
<tr>
<td>7-10</td>
</tr>
</tbody>
</table>

*Total dosage was administered in single infusions of 500 or 1000 mg iron as ferric carboxymaltose

For patients with a body weight <67 kg, single doses of 500 mg were given

Figure 2 Response Rates at Week 12. Primary (Hb increase ≥ 2 g/dL) and secondary (Hb increase ≥ 2 g/dL or normal Hb) end points [49]
Maintenance therapy

Despite successful treatment of IDA in IBD with IV iron, with or without EPO, anemia recurs frequently and surprisingly quickly. In their analysis of 88 patients from three prospective clinical trials, Gasché and co-workers demonstrated a recurrence of anemia in more than 50% of patients within one year [58], indicating the need for maintenance therapy. Based on these retrospective data, the authors initiated a prospective multicenter trial, in which patients who had successfully been treated with IV iron within the FERGICO trial [49], and who were non-anemic at the end of the study, were randomized to receive either ferric carboxymaltose (500 mg iron) bimonthly or placebo. The results of this 8-month study showed that the administration of FCM prompted by a fall in serum ferritin concentration to below 100 µg/L led to a significantly increased likelihood of avoiding anemia recurrence in IBD [59]. This study demonstrates for the first time that serum ferritin-triggered iron maintenance therapy is an effective and safe treatment strategy to prevent recurrence of anemia in patients who have responded to IV iron.

Erythropoiesis stimulating agents

In most IBD patients, treatment of the underlying disease in conjunction with iron, folic acid and vitamin B₁₂ supplementation is sufficient to effectively correct anemia. In patients showing an inadequate response to such therapy, however, treatment with ESAs is recommended [60]. A randomized clinical trial demonstrated that erythropoietin combined with IV iron was efficacious in correcting anemia in a majority of IBD patients, and this has been confirmed in other studies [34]. However, there are limited data on the exact dose and drug to be used, and in this rapidly developing field, the expertise of local hematologists or nephrologists can therefore be helpful [60].

Increased erythropoiesis leads to an increased demand for iron for the production of heme; iron supply is regarded as optimal when the transferrin saturation is calculated to be 30-40% and the serum ferritin concentration amounts to 200-500 µg/L. Since functional iron deficiency is always to be expected, therapy with erythropoiesis-stimulating agents should therefore always be accompanied by IV iron supplementation [4,12].

However, it should be kept in mind that the use of ESAs has been shown to be a risk factor for thrombosis [61,62], already a widespread complication of IBD and particularly of UC. Extensive experience in oncology and nephrology [63] suggests a therapeutic goal for ESA therapy of 11-13 g/dl hemoglobin. However, it is not clear whether this can equally be applied to the therapy of anemia in IBD patients. Figure 3 summarizes a treatment algorithm for iron replacement in IBD patients.

Blood transfusions

In the past, red blood cell (RBC) transfusion was relatively frequently carried out. However, despite significant reduction of the risk of infection, RBC transfusions are still associated with increased risks of venous and arterial thrombotic events, acute and delayed transfusion reactions, and transfusion-induced immunomodulation. Furthermore, red blood cells are an expensive and scarce resource. Therefore, the use of RBC transfusion should be restricted to very special clinical situations, i.e. acute severe anemia with hemodynamic instability, severe anemia-related weakness and fatigue, and/ or failure of all other treatments [12].

![Figure 3 Work-up for the management of iron deficiency anemia in patients with inflammatory bowel disease](image-url)
Conclusions

Anemia is the most prevalent extraintestinal complication of IBD and can substantially affect the quality of life of patients with IBD. Although there are several causes of anemia in IBD, IDA is the most common. Assessment of the iron status of patients suffering from inflammatory diseases, such as IBD, by using common biochemical values is insufficient. However, new indices of iron metabolism (i.e. TIR Index, reticulocyte hemoglobin content or percentage of hypochromic red blood cells) may help to improve the assessment of iron status in patients with IBD. The major goal when treating IDA in patients with IBD is first to supply sufficient iron to increase hemoglobin levels by >2 g/dL or increase them to normal values within 4 weeks and second to replenish iron stores (ferritin levels >100 g/L). Transferrin saturation levels >50% and ferritin levels >800 g/L are considered toxic and should be avoided. Besides, in patients with mild IDA and quiescent or clinical active IBD, IV iron should be the preferred route for iron supplementation. Figure 3 summarizes our current work-up for the management of IDA in patients with IBD.

References

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