Anemia and inflammatory bowel disease

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ABSTRACT

Anemia is a most common complication of inflammatory bowel disease. A high frequency of low hemoglobin values in these patients often leads physicians to subestimate this condition, which translates into ineffective treatment. On the other hand, the complex nature of anemia-inducing mechanisms in inflammatory bowel disease frequently raises doubt about the most appropriate therapy. A correct identification of patients with anemia, and adequate therapy are the essential pillars for improved quality of life. The right use of iron supplementation, and novel parenteral iron formulations, either with or without associated erythropoietin, have revolutionized our approach of this complication in the course of inflammatory bowel disease.

Key words: Anemia. Inflammatory bowel disease. Iron deficiency.

INTRODUCTION

Inflammatory bowel disease (IBD) is characterized by the involvement of the gastrointestinal tract and commonly other organs and systems. Hence we may divide the symptom spectrum of this condition into two major categories: Gastrointestinal disease proper and extraintestinal manifestations, among which anemia is highly prevalent.

When compared to other complications anemia has traditionally received little attention from gastroenterologists (1, 2). Inadequate control of patients with this complication has entailed a poorer quality of life (3, 4). In addition, lack of appropriate strategies for the treatment of anemia has resulted in increased morbidity (5, 6). This may be translated into higher transfusion requirements; average hospital stays, and needs for hospitalization.

This review will discuss the most relevant aspects regarding the etiology, diagnosis, and treatment of anemia in IBD. A literature search was performed of the Medline database in September 2007 using as search parameters the following key words: (“inflammatory bowel disease”
OR “Crohn’s disease” OR “ulcerative colitis”) AND (“anemia” OR “anaemia” OR “iron” OR “ferritin”).

ANEMIA DEFINITION AND IMPLICATIONS IN INFLAMMATORY BOWEL DISEASE

According to the World Health Organization, anemia is defined as the pathologic condition that arises when blood hemoglobin levels fall below 13 g/dL in males and 12 g/dL in females (7). This fall clinically manifests as symptoms including fatigue, exercise intolerance, headache, dyspnea, tachycardia, nausea, anorexia, weight loss, decreased libido, dizziness, tinnitus, reduced cognition, and reduced attention.

In IBD anemia has become highly relevant during the last ten years; it was believed to be a process inherent to IBD itself, and is now considered a well-defined condition in itself, partially dependent upon the underlying disease (8). A better understanding of anemia mechanisms has allowed the design of specific management strategies.

The most relevant causes of iron deficiency overall include malnutrition, parasitoses, and gynecological or digestive loss (the latter are most common in developed countries). Under normal conditions food provides 15-30 mg/day of elemental iron on average, and only 5-10% (1-3 mg/day) is absorbed by the bowel. There is a contraregulatory mechanism that increases or decreases iron absorption depending on parameters such as systemic deposits status, hematopoietic needs, or dietary concentrations. Iron metabolism homeostasis prevents ferric overload or a repeatedly negative balance. Such control occurs by increasing or decreasing iron absorption by the enterocyte, and iron release from stores.

Once the absorption threshold is exceeded, and iron reserves are depleted, the hematopoietic system is overcome by pathological losses, and serum hemoglobin falls. Thus, chronic unnoticed bleeding are the most significant cause of anemia in IBD (9). Anemia severity (there is consensus that anemia should be considered “severe” from 10 g/dL on) and onset speed will determine manifestations in each individual patient (1).

Digestive bleeding is not the only cause of anemia in patients with IBD. The activity of proinflammatory factors (cytokines characteristic of disease activity periods) should also be counted in, as these may influence bone marrow precursors and result in marrow failure, thus bringing about a “chronic disorder” anemia profile (10). Thus, depending on iron metabolism, anemia may present itself as an actual iron deficiency or a poor use of available iron. Other factors to consider in patients with IBD and anemia include malabsorption, presence of intestinal resections, malnutrition, use of drugs such as 5-aminosalicylates or thiopurine derivatives (azathioprine or 6-mercaptopurine), and hemolytic anemia. The presence of several concurrent factors in one patient is not an exceptional finding.

The exact prevalence of anemia in patients with IBD is unknown, but this complication is considered most common. Wilson et al. (11) estimate that 10 to 73% of outpatients and 30 to 70% of inpatients with Crohn’s disease have anemia. In the same study, in patients with ulcerative colitis prevalence was 9-37% for outpatients and 54% for inpatients. In both groups up to 31% of patients had hemoglobin levels corresponding to “severe” anemia (< 10 g/dL). The aforementioned authors highlight the high proportion of anemia patients with no specific treatment. In a more recent systematic review including mainly patients with Crohn’s disease similar prevalences are obtained (from 6 to 74%) (5).

Anemia is associated with reduced quality of life, and in most patients reduced hemoglobin is directly related to labor and cognition impairment (11,12). In the study by Wells et al. (4) oral or intravenous iron administration resulted in improved quality of life questionnaire scores (IBDQ/SF36), with a linear, significant correlation to hemoglobin levels. Similarly, other authors find this same association (2,3,13,14).

Vijverman et al. (15) described the basic characteristics of anemia in two cohorts of patients diagnosed with IBD ten years apart. Results showed that the characteristics (iron deficiency and chronic disorder) of “severe” anemia remained unchanged while the overall prevalence of anemia had decreased. The authors concluded that a greater recognition of the relevance of anemia in these patients, as well as the use of more potent drugs for its control, has led to a decrease in “mild” anemia rates, but “severe” anemia remains inadequately controlled.

ANEMIA-INDUCING MECHANISMS IN INFLAMMATORY BOWEL DISEASE AND SERUM MARKERS

We may consider that anemia in patients with IBD is most commonly a multiple-factor condition (16). However, for the sake of clarity, we shall discuss each mechanism separately.

Iron deficiency

Iron deficiency mainly results from sustained, most commonly unnoticed bleeding due to intestinal inflammation and permanent mucosal barrier disruption. Blood loss, rather than iron malabsorption, is the most common cause of iron deficiency in IBD (17).

Iron is absorbed mainly in the duodenum and proximal jejunum through the enterocyte’s apical and basolateral membrane. Once internalized, transportation to hematopoietic cells occurs via the binding of proteins, primarily transferrin. This protein, with a mean saturation of 30-40% of
its binding capacity under normal conditions, will carry iron to hematopoietic precursor cells and reticuloendothelial system deposits. In macrophages and dendritic cells iron accumulates as ferritin, and this is therefore the most reliable marker of systemic storage status in the absence of inflammation (18). On the other hand, ferritin is an acute phase reagent in proinflammatory settings, and increased ferritin levels under such circumstances may not reflect actual iron deficiency (19). Transferrin uptake by cells is mediated by a specific transferrin receptor (TfR) whose expression is ultimately regulated at the intracellular transcriptional level by feedback signaling, with expression being increased under intracellular iron deficiency conditions (20,21). In fact, its serum detectable truncated form, the soluble transferrin receptor (sTfR), is currently considered the most reliable parameter for iron deficiency detection in chronic inflammatory disease (8,22). Thus, increased sTfR levels suggest iron deficiency and elevated intramedullary erythropoiesis (23). In this respect, Guagnozzi et al. (24) posited the sTfR to log serum ferritin ratio as the best parameter for iron deficiency diagnosis, with a cut-off point at 1.5 in patients with no underlying iron deficiency disease, and lower than 0.8 under acute inflammation conditions (C-reactive protein higher than 5 mg/L). As sTfR measurement is not routinely performed in most centers, the authors (upon correlating serum sTfR to ferritin levels in the same patients) suggest a ferritin level lower than 28 ng/mL as the optimal cut-off for diagnosing iron deficiency in patients with IBD. Serum levels for the diagnosis of iron deficiency in patients with IBD will thus be altered by acute inflammation as typically seen in this condition (25).

Hemoglobinization will only occur in the presence of adequate intracellular iron levels (26). Iron shortage, together with increased systemic erythropoietin in the presence of ferropenic anemia, will result in ineffective erythropoiesis and the production of microcytic, hyperchromic red blood cells of varying size, which completely define the primary characteristics of anemia from iron deficiency (9).

**Chronic disorder anemia**

This is the second most common mechanism of anemia in IBD, with iron deficiency being usually concurrent. Chronic disorder anemia results from available iron misuse by hematopoietic precursors in the presence of normal or high total iron levels. This results from the fact that iron accumulated in deposits cannot be made to reach medullary precursors by the interaction of cytokines such as interleukin-6 (IL-6), which prevents iron from binding its plasma transporter (transferrin). In addition, IL-6 plays a role in blocking intestinal iron absorption (27-29). Phase reagents such as alpha, antitrypsin and IL-1 block transferrin uptake by erythroid precursors by inhibiting transcription for its specific receptors (TfR) (30). This accounts for low soluble receptor (sTfR) levels in chronic disorder anemia. On the other hand, iron uptake by dendritic cells and macrophages remains unchanged, and thus adequate iron levels exist in storage areas.

Additionally, a number of proinflammatory cytokines usually present in IBD may affect erythropoiesis. Tumor necrosis factor alpha (TNF alpha) and interferons types I and II block CFU-Es (colony forming units-erythroid) and BFU-Es (burst forming units-erythroid), and shorten RBC half-life (10). Interferon-gamma seems to be the most potent factor targetting CFU-E, whose differentiating and replicative capacity it fully blocks (31). Nitric oxide, in turn, not only inhibits erythroid progenitors but also blocks heme synthesis (32).

Erythropoietin levels in chronic disorder-related anemia are “inadequately” low for serum hemoglobin levels (33). Cytokines IL-6, TNF-alpha, and IL-1 have a negative influence on renal erythropoietin production (34). In addition, cytokines such as interferon gamma lower the response of precursors to erythropoietin, as seen in *in vitro* studies (31).

Table I shows the main biochemical differences between chronic disorder anemia and iron deficiency anemia, the two most common etiologies of anemia in patients with IBD.

**Vitamin deficiencies**

Vitamin B12, and folic acid deficiencies are causes of anemia with macrocytic RBCs. Only in extensive inflammatory conditions, in Crohn’s enteritis or in small-bowel resections may vitamin or iron deficiencies from malabsorption be anticipated (5). Folic acid, as is also the case with iron, is absorbed in the duodenum and jejenum. Most common causes of folate deficiency in IBD include malnutrition and drug interaction (methotrexate, sulphasalazine), with malabsorption being the major cause only exceptionally.

Vitamin B12 absorption requires two factors: First, the presence of stomach-derived intrinsic factor; second, a preserved healthy mucosa in the distal ileum. Inflammatory conditions here, typically Crohn’s ileitis or surgical resection involving this bowel segment, will result in a

### Table I. Biochemical changes in the differential diagnosis of iron-deficiency anemia and anemia from a chronic disorder

<table>
<thead>
<tr>
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<th>MCV, MCH</th>
<th>Serum iron</th>
<th>Transferrin-binding capacity</th>
<th>Serum ferritin</th>
<th>Marrow iron deposits</th>
<th>sTfR</th>
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<tr>
<td>Iron deficiency</td>
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<td>Chronic disorder</td>
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N: Normal; ↓: Reduced; ↑: Increased; MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; sTfR: Soluble transferrin receptor.
vitamin B<sub>12</sub> deficient status. Regular laboratory follow-up is needed in such situations, and specific parenteral vitamin supplementation should be considered for vitamin deficiency (35).

Anemia from drug-related toxicity

Inflammatory activity-controlling drugs are commonly used for IBD, which have side effects upon the marrow. Sulphazalazine and other 5-ASA drugs have been associated with hemolytic anemia, folate deficiency, and myelodysplasia (36). In turn, azathioprine and its derivative 6-mercaptopurin have direct myelotoxic effects (37-39). The usefulness of systematic thiopurin methyltransferase (TPMT) activity measurements has been considered for this phenomenon with controversial results (40). Intracellular accumulation of intermediate metabolites as a result of low enzyme activity is associated with increased adverse effects by medication. Thus, in patients with low TPMT activity levels, which occurs in up to 0.5% of the population (41), therapy would be contraindicated. On the other hand, normal TPMT activity does not release clinicians from their responsibility to follow up patients using laboratory tests, as these patients may also present with medullary adverse events on occasion. An increased mean corpuscular volume is commonly seen in patients on these drugs, which may “mask” the microcytic profile associated with underlying iron deficiency (5,42).

Hemolytic anemia

Several cases of hemolytic anemia associated with IBD have been reported (43,44) since Lorber et al. (45) first described it in 1955. The prevalence of positive Coombs tests in patients with IBD is estimated at 1.9%, but hemolysis parameters will be apparent in only 1.7% (46). Hemolytic anemia development is more common in patients with ulcerative colitis than in patients with Crohn’s disease. Crossed reactivity between surface colonocyte and RBC antigens is believed to be the main cause of this phenomenon (47). The course of hemolysis seems unrelated to bowel involvement, and may develop before the occurrence of gastrointestinal symptoms (43). Steroids are the first treatment option, followed by immunosuppressants. Colectomy with or without associated splenectomy should be considered for severe hemolysis and treatment failures (48).

Exceptional circumstances

Glucose-6-phosphate dehydrogenase deficiency, thalassemia, pernicious anemia from gastric involvement in Crohn’s disease (49), IBD-related liver disease, malabsorption due to bacterial overgrowth, and myelodysplastic syndromes are uncommon causes of anemia in IBD.

TREATING ANEMIA IN INFLAMMATORY BOWEL DISEASE

Anemia control and recovery in patients with IBD has a beneficial impact on quality of life indices (50). Our goal is to attain hemoglobin levels above 13 g/dL in males and 12 g/dL in females. Anemia is defined as severe in the IBD setting for hemoglobin levels below 10 g/dL. In this situation more aggressive initial therapies may be attempted, as discussed below. Once a therapy regimen has been initiated three responses may be described: Optimal, with hemoglobin above 2 g/dL; partial, with hemoglobin increased to 1 to 1.9 g/dL; and absent, with figures lower than 1 g/dL (1).

Additional strategies to approach the management of anemia should only be initiated after adequate inflammation control (5). Should disease activity be inadequately controlled, managing this complication will be much more difficult (5,51,52).

Three drug classes have been used for anemia control in IBD: Oral iron, parenteral iron, and erythropoietin (53).

Oral iron

Oral iron supplementation has traditionally included first-choice drugs for iron deficiency anemia in patients with IBD (5). Iron salts (fumarate, sulphate, glycinate) represent formulations providing the highest amount of iron for absorption by the intestinal mucosa (54). Available products provide iron amounts above the maximum absorption threshold, hence increasing oral doses will have no impact on greater absorption (55-57).

The response to enteral iron has always been considered slow and variable. Schröder et al. (13) found slower responses in ferritin store recovery for patients receiving oral iron versus patients on parenteral iron. However, in this same study, hemoglobin recovery rate in patients adequately responding to oral iron was no slower than that seen in patients receiving intravenous iron. Therefore, given the different cost-benefit profile of both therapies, defining the characteristics of patients eligible for either regimen becomes essential. When response to oral iron is partial or absent, or if oral iron is poorly tolerated, parenteral iron is a reasonable, effective alternative (4,51,58).

A particularly relevant difference between these two administration routes stems from their distinct tolerabili-
ty. Iron sucrose, with a better safety profile when compared to previous parenteral formulations, stands out because of better tolerability versus oral forms (13).

Silva et al. (59) studied oral iron tolerability among patients with and without IBD, and found no greater incidence of adverse effects in any group. This study also analyzed inflammatory activity parameters in patients with IBD on oral iron, and found a poorer clinical activity in the subgroup of patients with ulcerative colitis (6%), but not in patients with Crohn’s disease. Authors highlight that no increased activity for endoscopic, histologic, or serologic indices, or mucosal oxygen-reactive metabolite production were found, as was also the case with serum antioxidant levels. Symptom exacerbation as reflected by this paper in ulcerative colitis patients is not exclusive feature of this condition, and the same author described exacerbations in patients with Crohn’s disease receiving oral iron in a retrospective study (60).

The role of oral iron as an intestinal mucosal oxidant, and its potential association to IBD exacerbation have been discussed by Erichsen et al. (61-63). These authors demonstrated that, after administering iron salt supplementation for one week to 10 patients with Crohn’s disease and 10 healthy controls, serum antioxidants (glutathione and reduced cysteine) decreased more in the former. In turn, baseline inflammatory activity indices were seen to increase. This fact suggests a somewhat pro-oxidating effect of iron both locally and systemically, but increased inflammatory activity secondary to its administration remains controversial. In fact, studies with a higher number of patients and longer follow-up periods find no significant association (59,60).

Parenteral iron

Parenteral iron administration prevents many of the issues associated with oral iron ingestion from arising. Thus, it avoids the limiting step of bowel absorption, which allows a fast availability of 100% of administered iron at marrow level. Secondly, no gastrointestinal adverse events arise, which are commonplace for oral formulations and to a great extent responsible for iron salt intolerance (59,60). On the other hand, adverse reactions traditionally found when administering parenteral iron are now avoided by the introduction of more stable and effective transporters, including iron sucrose, which allows complete storage reposition with few infusions (53).

Indications have been established for the use of intravenous iron supplementation (64): Patients with severe anemia (hemoglobin < 10 g/dL), patients with excessive loss due to slow reposition with oral therapy (65), malabsorption, and patients with iron deficiency who do not tolerate or respond to oral iron. Regarding the latter indication, Bodemar et al. (51) demonstrated that up to 91% of patients with IBD and prior oral iron intolerance responded satisfactorily to iron sucrose infusion. Patients with anemia and IBD may commonly meet more than one of the above criteria.

Given their historical importance we shall briefly discuss all three parenteral iron forms, even if only the third is to be used given its high safety and efficacy (66).

— Iron dextran: The oldest formulation. It consists of a high-molecular-weight colloidal iron hydroxide solution with a dextran polymer. Its main advantage over the other preparations is that loss reposition may be achieved with only one dose, with intramuscular injection being an additional option. The latter is not recommended because of erratic absorption, pain, and local tattoo effect. Frequent adverse effects, including fatal reactions, represent their main drawback (67).

— Iron gluconate: Assimilation is more effective with this iron form, as it is directly delivered to plasma proteins (apoferitin, apotransferrin) with no in-between steps needed. Adverse reaction rates, while lower than with iron dextran, reach up to 35%, and serious reactions amount to 0.04% (68).

— Iron sucrose: FDA-approved in 2000, its use has become widespread. A molecular weight between 34,000 and 60,000 Daltons, and high water solubility confer properties such as rapid tissue diffusion and high bioavailability, with a plasma half-life of 6 hours. It conjugates with plasma proteins in 1-2 minutes, and may be identified in the liver and bone marrow in fewer than 5 minutes. This profile makes it highly effective in directly delivering iron to erythroblasts, and very safe with no cross-reactions, in contrast to other parenteral formulations (69). Infusion rate should not exceed from 20 mg/min, and administration exclusively occurs through the intravenous route. Overall adverse event rates are somewhat smaller than with gluconate formulations, and no fatal reaction has ever been reported (64). Doses usually recommended for adults are 200 mg i.v. twice a week up to the total amount estimated based on iron deficiency estimations. Such estimates are performed using the formula (70):

Iron deficiency (mg) = [Weight (kg) x (Target hemoglobin – Current hemoglobin (g/dL))] + 500 (estimated storage deficiency for iron reposition)

The goal is reaching hemoglobin levels around 13 g/dL for males or 12 g/dL for females, and ferritin levels above 50 ng/dL (14,71).

Adverse effects of parenteral iron infusion include: Blood pressure changes, metallic taste, bradycardia, chest pain, headache, abdominal pain, nausea, vomiting, diarrhea, fever, pruritus, joint and muscle pain. These symp-
toms develop only occasionally following iron sucrose infusion. To minimize potential adverse events the maximum recommended dose should not be exceeded and infusion rates should be complied with.

In an attempt to define biochemical parameters predictive for response to parenteral iron, Gasche et al. (72) performed a prospective study in 103 patients with IBD and severe anemia (mean hemoglobin around 8.8 g/dL). Patients were administered on average 1,200 mg i.v. of iron sucrose in six doses, and a satisfactory response (mean hemoglobin increase by 3.2 g/dL) was seen in 65% of patients, whereas a partial response (hemoglobin increase by 1.2 g/dL) in the remaining 35%. When baseline laboratory parameters were analyzed for responders, the likelihood of a complete response to i.v. iron therapy reached 80% in patients with erythropoietin above 166 U/L, sTfR > 75 nmol/l, and transferrin > 3.83 g/L.

**Erythropoietin**

Recombinant human erythropoietin (rHuEPO) has been successfully used together with intravenous iron for anemia in association with chronic renal failure (73). In chronic disorder-related anemia supraphysiological erythropoietin doses have been shown to overcome the theoretical sensitivity threshold of erythroblasts (inhibited by proinflammatory cytokines), and to allow erythropoiesis with no significant adverse effects (74,75). Because of cost-benefit reasons rHuEPO should be reserved for patients with no adequate response to parenteral iron, which occurs in around one third of patients with anemia and IBD (2).

The addition of erythropoietin to an intravenous iron regimen was analyzed in a prospective study of 39 patients with IBD irrespective or intolerant to oral iron (76). Patients were randomized between two groups—the first group received iron sucrose i.v. plus placebo, the second group received iron sucrose i.v. plus rHuEPO (at a dose of 150 IU/kg s.c.) for 16 weeks. A greater, faster increase in hemoglobin levels was seen in the rHuEPO group. In 5 patients unresponsive to i.v. iron alone a response was obtained when rHuEPO was used as add-on. On the other hand, the only patient in the rHuEPO group who did not respond in a complete manner ultimately did so when doses were titrated to 300 IU/kg.

From this study and other similar investigations (58,77-80) it may be concluded that rHuEPO is a reasonable alternative for chronic disorder anemia in association with IBD who do not respond to iron therapy alone (81).

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**Fig. 1.** Anemia treatment in patients with inflammatory bowel disease (Hb: Hemoglobin; EPO: Erythropoietin; sTfR: Soluble transferrin receptor).
CONCLUSIONS

Anemia in IBD is a common complication requiring effective action by clinicians due to its relevant impact on patient quality of life. This complication should be considered an extraintestinal in its own right. Given the frequent multifactorial nature of anemia we shall consider before treatment onset and from a practical standpoint whether the patient’s anemia stems from iron deficiency or chronicity itself. Importantly, our efforts to correct anemia should rely on adequate inflammation control, in the absence of which no proper approach to this condition is feasible. Figure 1 shows a schematic of the most appropriate therapy for the management of anemia in IBD. The ultimate goal is an increase in hemoglobin levels that may be translated into improved quality of life for our patients.

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