TOPIC HIGHLIGHT

Anemia in inflammatory bowel disease: A neglected issue with relevant effects

Danila Guagnozzi, Alfredo J Lucendo

Danila Guagnozzi, Alfredo J Lucendo, Department of Gastroenterology, Hospital General de Tomelloso, 13700 Tomelloso, Ciudad Real, Spain
Author contributions: Both authors contributed equally to this paper.
Correspondence to: Danila Guagnozzi, MD, Department of Gastroenterology, Hospital General de Tomelloso, Vereda de Socuéllamos, s/n. 13700 Tomelloso, Ciudad Real,
Spain. danila_g@libero.it
Telephone: +34-926-525926 Fax: +34-926-525870
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Abstract

Anemia, a common complication associated with inflammatory bowel disease (IBD), is frequently overlooked in the management of IBD patients. Unfortunately, it represents one of the major causes of both decreased quality of life and increased hospital admissions among this population. Anemia in IBD is pathogenically complex, with several factors contributing to its development. While iron deficiency is the most common cause, vitamin B_{12} and folic acid deficiencies, along with the effects of pro-inflammatory cytokines, hemolysis, drug therapies, and myelosuppression, have also been identified as the underlying etiology in a number of patients. Each of these etiological factors thus needs to be identified and corrected in order to effectively manage anemia in IBD. Because the diagnosis of anemia in IBD often presents a challenge, combinations of several hematimetric and biochemical parameters should be used. Recent studies underscore the importance of determining the ferritin index and hepcidin levels in order to distinguish between iron deficiency anemia, anemia due to chronic disease, or mixed anemia in IBD patients. With regard to treatment, the newly introduced intravenous iron formulations have several advantages over orally-administered iron compounds in treating iron deficiency in IBD. In special situations, erythropoietin supplementation and biological therapies should be considered. In conclusion, the management of anemia is a complex aspect of treating IBD patients, one that significantly influences the prognosis of the disease. As a consequence, its correction should be considered a specific, first-line therapeutic goal in the management of these patients.

Key words: Anemia; Inflammatory bowel disease; Iron deficiency; Anemia of chronic disease; Erythropoietin

Core tip: Anemia represents one of the major causes of both decreased quality of life and increased hospital admissions among inflammatory bowel disease (IBD) patients. This paper analyses the complex etiological and pathophysiological mechanisms underlying anemia in IBD, including iron and micronutrients deficiency, effects of proinflammatory mediators and bone marrow insufficiency secondary to the disease by itself and IBD therapy. By a comprehensive review of the current diagnostic and therapeutic evidences on anemia in IBD, an state-of-the-art approach will be provided to effectively manage this challenging and common condition.

INTRODUCTION
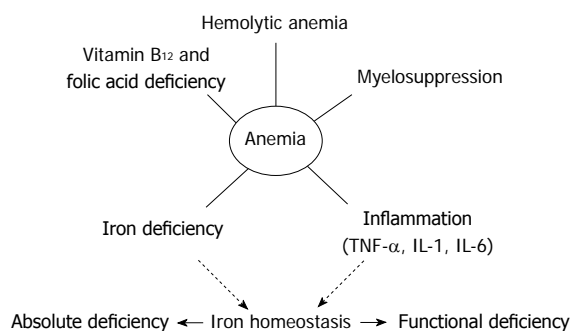
Anemia, a frequent systemic complication in patients

Figure 1 Pathogenesis of multifactorial anemia associated to inflammatory bowel disease. TNF-α: Tumour necrosis factor-α; IL: Interleukin.

with inflammatory bowel disease (IBD), has a complex and multifactorial pathogenesis (Figure 1). It is considered a prototype of a combination of iron deficiency (IDA) and anemia of chronic disease (ACD), which is caused by the negative effects of an activated immune system at different levels of erythropoiesis[1,2]. Besides IDA and ACD, metabolic disturbances, vitamin deficiencies, and various drug therapies commonly used in IBD can aggravate anemia in IBD patients[3]. The study of anemia in these patients thus requires a specific diagnostic and therapeutic approach.

It is important to highlight that anemia has a significant impact on the disease and is one of the most frequent comorbid conditions associated with mortality in IBD patients[4]. In addition, it also has a relevant effect on health related quality of life (QoL) and ability to work[5,6]. The fact that it is also a common cause of hospitalization and delay of discharge[7] only serves to underscore the need for prompt diagnosis and management of this condition.

Although the correction of anemia in IBD patients can improve the QoL and the quality of patient management, the specific diagnosis and treatment of anemia is often a low priority for gastroenterologists and has thus received little attention. A recent study showed that further diagnostic tests were undertaken in only one-third of patients with proven anemia and that 54.3% of patients diagnosed with IDA receive no iron supplements[8,9].

This article reviews current data on the diagnosis and treatment of anemia in IBD patients. A search was conducted in the PubMed, Cochrane, MEDLINE, and Scopus libraries with the following individual and combined key words: Crohn's disease, ulcerative colitis, anemia, iron deficiency anemia, anemia of chronic disease, vitamin B12 deficiency, folic acid deficiency, myelodysplastic syndrome, refractory anemia, iron supplementation, intravenous iron therapy, erythropoietin, and inflammatory bowel disease. References cited in the articles retrieved were also searched in order to identify other potential sources of information. The results were limited to human studies available in English.

PREVALENCE OF ANEMIA IN INFLAMMATORY BOWEL DISEASE

The prevalence of anemia in IBD is markedly variable, ranging from 6% to 74% in two systematic reviews[10,11]. The more recent review calculated a mean prevalence of 17% (16% in outpatients and 68% in hospitalized patients), with anemia occurring more frequently in patients with Crohn's disease (CD) than in those with ulcerative colitis (UC)[3,12]. This variability in the prevalence of anemia depends on different factors. First, the definition of anemia is not homogenous in the various studies reviewed. In fact, because the widely accepted World Health Organization criterion for the diagnosis of anemia [hemoglobin (Hb) below 13 g/dL in men or 12 g/dL in non-pregnant women][13] has been questioned due to racial differences, environmental conditions, and eating habits[14,15], its use cannot completely reflect the real prevalence of anemia in different IBD populations. Furthermore, estimations of the prevalence of anemia often depend on the specific groups of patients studied (for example, hospitalized patients *vs* outpatients). In this sense, a study from a Swedish cohort showed that the prevalence of anemia in hospitalized UC and CD patients was higher than among outpatient populations (5% *vs* 35% and 9% *vs* 50%, respectively)[16]. Furthermore, it is important to note that anemia has been poorly studied in pediatric IBD patients. One recent epidemiological study showed that while the prevalence of anemia was 72% at the time of diagnosis, the proportion of severely anemic pediatric patients decreased from 34% to 9% while the number of patients with mild anemia doubled after 1 year of follow-up[17]. Finally, because Hb levels form part of a widely used disease activity index, the presence of anemia correlates directly with disease activity, which means that the prevalence of anemia may change throughout the natural history of the disease. In fact, the prevalence of mild and moderate anemia in IBD has decreased over time, reflecting improved treatment and management of the disease. However, the prevalence of severe anemia in IBD patients over the last 10 years has not decreased in the same manner[18].

PATHOGENESIS OF ANEMIA IN INFLAMMATORY BOWEL DISEASE

Iron deficiency anemia

Iron deficiency is the most common cause of anemia in IBD patients, with a reported prevalence of up to 90%[11]. Iron deficiency may be related to "absolute iron deficiency" due to low dietary intake and blood loss from ulcerated intestinal mucosa (especially in UC patients) along with reduced iron absorption (especially in CD localized in the upper GI tract), or it may be related to "functional iron deficiency."

Iron is an essential mineral for the function of all

body cells and is absorbed at the apical surface of enterocytes to be transported by ferroportin across the basolateral surface of the enterocyte into the circulation[19]. In the maintenance of iron homeostasis, the peptide hormone hepcidin is a master regulator that is produced in response to iron overload or upon induction by pro-inflammatory stimuli such as lipopolysaccharide or interleukin (IL)-6. In fact, inflammatory conditions can interfere with iron absorption by causing an increase in hepcidin that inhibits ferroportin activity[20], leading to its internalization and degradation[21]. The inhibition of ferroportin activity blocks the transfer of absorbed iron from the enterocyte into the circulation and causes iron retention in the macrophages and monocyte cells[22]. In addition, during inflammation other events contribute to the retention of iron in these cells, including the inhibition of ferroportin transcription by pro and anti-inflammatory cytokine action and a reduction in the half-life of erythrocytes due to oxidative stress and lipid-peroxidation, with iron recycling through erythrophagocytosis[23]. These mechanisms all lead to "functional iron deficiency," which means that despite an abundance of iron in the body, it is not available for erythropoiesis.

Anemia of chronic disease

The exact prevalence of ACD in IBD patients is unknown[24], with its etiology being ascribed to altered erythropoiesis at different levels[25]. Firstly, chronic inflammation can decrease erythropoiesis by direct action of interferon (IFN)-γ, IFN-α, tumor necrosis factor (TNF)-α, and IL-1 in the bone marrow to exert pro-apoptotic effects on erythroid burst-forming units (BFU-E) and colony-forming units (CFU-E)[26]. Moreover, IL-1, IL-6, TNF-α, and hepcidin may decrease erythropoietin (EPO) synthesis and impair its biological activity[1,27]. In fact, EPO levels in ACD have been found to be inadequate in some chronic disease and IBD patients[11,28,29]. Low EPO production is due to direct inhibition of the activity of the promoter of the EPO gene by IL-1 and TNF-α, which in turn inhibits the synthesis of EPO in the kidney and acts indirectly on EPO-producer cells through cytokine-induced toxic radicals[30]. Impairment of the biological activity of EPO means that much higher amounts of EPO are needed to restore the formation of CFU-E in the bone marrow. Cytokines can also interfere with the signaling process mediated by the interaction of EPO and its receptor and can down-regulate EPO receptors on erythroid progenitor cells[26], thus producing cell resistance to EPO activity. Finally, the limited availability of iron for heme biosynthesis induced by "functional" or "absolute" iron deficiency and the inhibition of iron uptake into erythroid progenitors due to the blocking of the transferrin receptor by alfa1-antitrypsin (an acute phase protein) negatively affect the biological functions of EPO along with cell growth and differentiation[1].

Other types of anemia

Vitamin B12 deficiency has been observed in 48% of CD patients and in 5% of UC patients[31] while folic acid deficiency has been noted in 67% of CD patients and in 30%-40% of UC patients[31-33]. These types of deficiencies depend on low dietary intake as well as increased turnover of epithelial cells due to chronic inflammation in the intestinal mucosa and a reduced absorption in the intestinal tract[34-36]. In CD, several factors influence these deficiencies, including the inflammatory involvement of ileal mucosa, the presence of fistulas, secondary bacterial overgrowth with direct consumption of vitamin B12, and extensive surgical resections in small bowel segments with impaired absorption[37]. Deficiencies in patients with UC derive from proctocolectomy and ileo-pouch anastomosis, with the prevalence of vitamin B12 deficiency being affected more by surgical changes leading to impaired function of ileal receptors, reduced intestinal transit time, and secondary bacterial overgrowth than on the length of the ileal segment resected[38].

Autoimmune hemolytic anemia (AIHA) is a rare type of anemia observed in UC patients. It can be due either to the development of antibodies with cross-reactivity with erythrocytes[39] or to the hemolytic effect of sulfasalazine in patients with glucose-6-phosphate dehydrogenase deficiency[40]. This association was first described in 1955 by Lorber *et al*[41] with the most recent studies calculating that the prevalence of AIHA in UC patients is between 0.2%-1.7%, as indicated by a positive Coombs test result in 1.8% of patients studied[40]. AIHA can occur before, after, or at the moment of diagnosing UC. Even when the potential relationship between disease activity and the occurrence of AIHA is not clear, a correlation with the extension of the disease has been demonstrated in several reports, which show a prevalence of AIHA of up to 28% in patients with extensive colitis[40].

Anemia can also represent a late manifestation of myelosuppression in IBD patients due to several factors. Firstly, myelosuppression can be associated with myelodysplastic syndrome (MDS), with ineffective erythropoiesis and a risk of progression to acute myeloid leukemia. Some studies have shown a frequent predominance of MDS in CD with colorectal involvement; however, it should be noted that the prognosis of IBD with concomitant MSD is determined by the MSD itself[42]. The prevalence of MDS in IBD patients has been estimated to be 0.17%, with a higher incidence in IBD patients than in the general population (170/100000 IBD patients/year *vs* 20-30/100000 of the general population over the age of 70/year)[43]. This is probably due to a undetermined common pathogenetic mechanism, the long-term use of immunosuppressive drugs, or chromosomal abnormalities in bone marrow cells that have been observed in 67% of patients with concomitant IBD and MSD[44,45]. These can induce the development of colitogenic monocytes, producing a large number of pro-inflammatory cytokines resistant to apoptosis upon stimulation with microbial antigens. Indeed, one of the first hypotheses about this association regarded IBD to be an extra-hematologic manifestation of MSD with a

Table 1 Laboratory findings in anemia of inflammatory bowel disease patients

Biomarkers	IDA	ACD	Mixed anemia
MCV (fL)	< 80	Normal or reduced	Normal or reduced
MCH (pg)	< 27	Normal	Normal
CHr (pg)	< 28	Normal	Normal
C-RP (mg/dL)	Vormal	> 5	> 5
ferritin (ng/mL)	< 30	> 100	30-100
TfS (%)	< 20	< 20	< 20
Ferritin index	> 3.2	< 11	> 2
sTfR	Increased	Normal	Normal or increased
Hepcidin (nmol/L)	Reduced	Increased (> 4)	Increased (> 4)

MCV: Mean corpuscular volume; MCH: Mean corpuscular hemoglobin; CHr: Reticulocyte hemoglobin content; C-RP: C-reactive protein; TfS: Transferrin saturation; sTfR: Soluble transferrin receptor; IDA: Iron deficiency anemia; ACD: Anemia of chronic disease.

vasculitic process at the level of the mesenteric arteries[46]. Alternatively, myelosuppression may represent a complication of severe UC with the development of a systemic inflammatory response syndrome, or even been a side effect of immunosuppressive drugs. There is an increasing concern about therapy-induced leukemias and myelodysplastic syndromes in patients treated with thiopurines, which are extensively used as immunosuppresants in IBD, particularly for maintenance therapy[47]. Data from a large French cohort of patients (19486) with inflammatory bowel disease identified a relative risk of developing lymphoproliferative disorders as 5.2 for patients who were treated with thiopurines compared to those who were not[48].

Finally, additional gastrointestinal diseases that do not usually cause bleeding should be also considered in case of iron deficiency anemia in those IBD patients who maintain disease into remission, including colon or gastric cancer o polyps, peptic ulcer, hiatal hernia with linear erosions, atrophic or *Helicobacter pylori*-associated gastritis, and celiac disease[49,50].

DIAGNOSIS OF ANEMIA IN INFLAMMATORY BOWEL DISEASE

Basic laboratory screening for anemia in IBD should consist of hemoglobin and full blood counts (including reticulocytes to differentiate between regenerative or hypo-regenerative anemia), with a determination of erythrocyte mean corpuscular volume (MCV) to distinguish between microcytic, normocytic, and macrocytic anemia as well as a determination of mean corpuscular Hb (MCH) and reticulocyte Hb content (CHr), if available. Moreover, assessments of both the level of inflammation by means of C-reactive protein (CRP) and of iron status are required. There is no single biomarker to diagnose iron deficiency in IBD; a combination of different biomarkers is needed. In most cases, total store of body iron with serum-ferritin (or ferritin) and the iron available in the bone marrow with transferrin saturation (TfS) is sufficient to differentiate between IDA and

ACD[51]. However, many of the laboratory measures of iron status may be unreliable in IBD patients because the inflammation influences all parameters of iron metabolism to produce "functional iron deficiency[52,53]". For this reason, in some cases it is essential to use other, more specific biomarkers of iron status to allow for the differentiation between predominantly IDA, predominantly ACD, and ACD combined with iron deficiency in order to provide appropriate, more effective treatment[54] (Table 1). Further testing for causes of anemia in IBD may include tests for vitamin B12, folic acid (especially erythrocyte levels, which, when available, represent the best stable marker of folic acid deficiency), haptoglobin, lactate dehydrogenase, indirect bilirubin (with Coombs test if hemolytic anemia is confirmed), and serum creatinine in order to rule out potential hemolysis or renal failure, which in itself can cause macrocytic or normocytic anemia[51]. It should be noted that if the origin of anemia is not obvious, IBD patients should be tested for MDS, especially if normocytic and hypo-regenerative anemia are both present, carrying out a bone marrow study in selected patients.

Once a diagnosis of IBD has been established, patients in clinical remission should be screened for anemia at least every 6 to 12 mo, whereas patients with active disease should be tested every 3 mo or at even shorter intervals, depending upon their iron status[55].

Iron deficiency anemia
Patients are considered to suffer from IDA when they present with low Hb (men < 13 g/dL, non-pregnant women < 12 g/dL), TfS < 20%, and ferritin concentrations < 30 ng/mL without any biochemical or clinical signs of inflammation. A low MCH (< 27 pg) or even better a low CHr (< 28 pg) rather than MCV (< 80 fL) have became the most important red cell markers for detecting iron deficiency in circulating red blood cells. Although MCV is a reliable and widely available measurement, it tends to be a relatively late indicator in patients who are not actively bleeding[56]. A normal Hb level does not rule out iron deficiency and with an MCH in the lower limit of normal (normal range: 28-35 pg) or an increased red cell distribution width (RDW, normal range: 11-15), one can suspect the presence of mild iron deficiency without anemia[57]. Although the main laboratory marker for iron deficiency with or without anemia is a low ferritin level (< 30 ng/mL) in the absence of inflammation, in the presence of inflammation a normal ferritin level (as an acute phase reactant) does not rule out iron deficiency; therefore, TfS should also be measured. "Functional iron deficiency" in inflammatory conditions should be defined by low TfS (< 20%) and normal ferritin concentration (> 100 ng/mL), whereas low TfS (< 20%) and intermediate ferritin values (30-100 ng/mL) suggest "absolute iron deficiency[57]". Some authors suggest a cut-off value of TfS < 16% combined with low iron value for the diagnosis of iron deficiency[51]. Iron deficiency can also be defined by a ferritin index > 3.2 (> 2 if CRP > 5 mg/L). The ferritin index, which reflects

the iron supply for erythropoiesis, is calculated as the ratio between the soluble transferrin receptor (sTfR) and the log of ferritin[58]. The sTfR is a truncated fragment of the membrane receptor and its levels increase when the availability of iron for erythropoiesis is low, as occurs in IDA. CHr, which measures the Hb content of reticulocytes, reflects the direct measurement of available iron for erythropoiesis and is useful for differentiating IDA from ACD. In particular, CHr has a high sensitivity and specificity for diagnosing iron deficiency and is less affected by inflammation than TfS and ferritin, but no data are available for its use in IBD[58].

Anemia of chronic disease

Patients are considered to suffer predominantly from ACD when they present evidence of inflammation (with increased levels of serum CRP and clinical signs), an Hb concentration < 13 g/dL for men and < 12 g/dL for non-pregnant women, and a low TfS < 20%, but normal or increased ferritin concentrations > 100 ng/mL. In the presence of intermediate ferritin concentrations (30-100 ng/mL), a diagnosis of ACD combined with "absolute iron deficiency" is confirmed if the ferritin index has a value < 2 with normal CHr[54,58-60]. Still, some cases may require supplementary testing for the differential diagnosis between IDA and ACD. It has recently been shown that hepcidin levels may replace the ferritin index for the confirmation of combined IDA and ACD if the hepcidin levels are > 4 nmol/L with a CHr < 28 pg[61]. In fact, hepcidin levels have been found to be significantly higher in IBD patients compared with healthy controls, with a significant correlation with ferritin levels, CRP, and disease activity, whereas those of prohepcidin were observed to be significantly lower[62]. In addition, although other hematological indices may help in the diagnosis of iron deficiency in ACD, many of them are only available in specific hematology analyzers and their precise clinical usefulness has yet to be determined. In a recent study carried out with a Beckman-Coulter LH 780, high values of RDW and low values of blood cell Size Factor were the best markers for the diagnosis of IDA, whereas both Reticulocyte Distribution Width-Coefficient of Variation (RDWR-CV) and Reticulocyte Distribution Width-Standard Deviation (RDWR-SD) were significantly correlated to disease activity and CRP levels[63].

TREATMENT OF ANEMIA IN INFLAMMATORY BOWEL DISEASE

Iron supplementation

Iron supplementation should be considered in every patient presenting iron deficiency with or without anemia. In patients with mild to moderate anemia (Hb ≥ 10 g/dL), the administration of oral iron at optimal low doses of 60-120 mg/d is the conventional approach recommended by the Centers for Disease Control and Prevention[9,64]. Oral iron compounds are mostly available as inorganic ferrous salts, such as ferrous fumarate, ferrous

sulphate, and ferrous gluconate containing 33%, 20%, and 12% of elemental iron, respectively. A single tablet of most of these ferrous salt preparations provides a sufficient dose for the treatment of iron deficiency[65,66]. In fact, there is no evidence to support the administration of high doses of iron in comparative trials[65-67]; on the contrary, excessive doses may actually decrease tolerance and compliance while increasing gastrointestinal side effects, with a discontinuation of iron treatment in 20% of patients with or without IBD[68]. Nevertheless, there are several drawbacks associated with oral iron therapy that must be taken into account. In addition to the generally low bioavailability of oral iron, intestinal absorption is further compromised in IBD patients due to an inflammation-driven blockade caused by increased hepcidin levels. For this reason, in patients with active inflammation and combined ACD/iron deficiency, intravenous administration of iron may be preferable to oral iron therapy. Moreover, when achieved, the therapeutic effect of oral iron supplementation is slow, requiring two to three weeks to obtain increased Hb concentrations and up to two months to achieve normal values. At least six months are needed to replenish iron stores completely[69]. Moreover, non-absorbed iron salts can be toxic to the intestinal mucosa and oral iron has been shown to increase intestinal inflammation and possibly colon carcinogenesis in animal models through the production of reactive oxygen species that mediate intestinal damage and the alteration of the intestinal bacterial milieu in rodents[70-75].

Intravenous iron therapy is more effective, has a higher response rate, and is better tolerated by patients, with a lower discontinuation rate due to adverse events than oral iron supplementations in IBD patients, as demonstrated in a recent systematic review with meta-analysis[76]. However, it is important to highlight that of 757 articles identified, only three industry-funded articles met the inclusion criteria for this systematic review[69,77-83]. Nevertheless, intravenous iron therapy should be considered in patients with severe anemia (< 10 g/dL), with intolerance or inadequate response to oral iron, or with concomitant erythropoietin treatment and/or presence of active IBD. It should be noted that the new intravenous iron formulations (iron carboxymaltose, iron ferumoxytol, and iron isomaltoside) reduce both the risk of free iron reactions as well as that of immunogenicity without the need for administering a test dose before starting treatment. Treatment duration is also reduced because the new formulations are safer at higher doses than traditional intravenous iron formulations (iron sucrose, ferric gluconate, and low molecular weight iron dextran). Iron carboxymaltose is the only new intravenous iron formulation approved for use in Europe that has been studied in IBD patients. Its superiority at higher standardized doses over individually calculated doses of iron sucrose has been demonstrated along with its efficacy in reducing anemia recurrence as compared to a placebo[84-86]. After 12 wk of follow-up,

ferric carboxymaltose led to higher response rates (66.1% *vs* 54.1%), a higher proportion of non-anemic patients (72.8% *vs* 61.8%), and better treatment adherence (92.5% *vs* 79.1%) than iron sucrose, with no difference in treatment-related adverse events (13.9% *vs* 11.3%). With regard to side effects, in the ferric carboxymaltose group there were more skin and subcutaneous tissue disorders (rash, dermatitis, pruritus) and more cases of hypophosphatemia, but fewer infusion site reactions than in the iron sucrose group. The superiority of high-dose intravenous iron supplementation in IBD probably depends on the iron overload produced in the macrophages of the reticulo-endothelial system. This induces an overexpression of ferroportin, which may, in turn, by-pass the hepcidin block in ACD[57]. Recently, an alternative dosage scheme to the traditional Ganzoni formula has been presented for ferric carboxymaltose treatment. In the new protocol, for a baseline Hb > 10 g/dL, the dose is 1.0 g for patients with a body weight < 70 kg and 1.5 g for patients > 70 kg; the corresponding total doses for serum Hb ⩽ 10 g/dL are 1.5 g and 2.0 g[84]. Phase 3 clinical trials are currently underway to evaluate the use of ferumoxytol in patients with iron deficiency anemia, including a subgroup with IBD (ClinicalTrial.org identifier: NCT01114139, NCT01114217 and NCT01114204). However, ferumoxytol may be problematic in IBD patients because it can interfere with MRI signals due to the paramagnetic nature of its iron core[19]. In addition, a Phase 3 clinical trial of iron isomaltoside (NCT01017614) and a Phase 4 study of iron sucrose (NCT01067547) are currently being carried out on IBD patients with IDA. All treatments being tested strive to achieve ferritin concentrations > 100 μg/L, measured as early as 8 wk after intravenous iron treatment to obtain a reliable result[55]. Considering that the recurrence of iron deficiency with or without anemia is frequent in IBD patients[87], regular controls at 12 wk intervals are advisable so that treatment can be restarted promptly if needed.

Erythropoietin supplementation

Several studies have shown that recombinant human erythropoietin may be effective for treating ACD in IBD patients[88-95]. In the anemia treatment algorithm, intravenous iron therapy should be considered as a first-line therapy in patients with severe anemia whereas erythropoietin treatment should be considered only in patients unresponsive to intravenous treatment, with low EPO levels, or who are unresponsive to aggressive management of IBD[29,53,96] since EPO can be used as an adjunct therapy to control the inflammation[97]. Recently, a prospective study on CD patients showed that EPO combined with enteral nutrition can improve the Hb levels in CD patients with a treatment success rate of 63.16% in the EPO group compared to none of the patients in the non-EPO group[98]. When a decision has been made to administer EPO therapy, it should always be combined with intravenous iron supplementation to meet the increased demand caused by the "functional iron deficiency" typical in IBD patients[99].

Other treatments

Intramuscular vitamin B12 continues to be the gold standard therapy for vitamin B12 deficiency, especially in symptomatic patients[100]. A dose of 1000 μg/wk for 8 wk, then 1000 μg once monthly for maintenance lifelong is recommended[101]. No therapeutic advantages have been demonstrated for either cyanocobalamine or hydroxycobalamine in terms or serum levels during maintenance therapy[102]. Effectiveness data for sublingual[103,104] and intranasal[105] routes for vitamin B12 administration have revealed as promising non-invasive alternatives.

Specific treatment of IBD has been shown to gradually increase Hb levels over time, which indicates that the presence of anemia is positively associated with disease activity and disease-associated gut lesions. Some data suggest that anti-TNF-α treatment improves the anemia in a sub-group of patients with CD. In fact, patients who responded to treatment showed improvements in their anemia within 2 wk of the first infusion of Infliximab, with a parallel improvement in their CD activity index and an increase in endogenous EPO levels over time[12]. Infliximab seems to neutralize the inhibitory effects of TNF-α on EPO production, increasing the availability of iron for erythropoiesis and reducing anemia[30]. The drug produces these effects through various mechanisms, including reduced cytokine-induced formation of ferritin and hepcidin, with improvement of intestinal iron absorption and iron release from macrophages *via* ferroportin-mediated iron export[21,106,107]. Moreover, Infliximab improved the proliferation of cultured BFU-E, blocking the inhibitory effects of cytokines on erythroid progenitor cells[26]. Finally, it induced mucosal healing, thereby reducing the production of pro-inflammatory cytokines and the amount of blood loss through mucosal ulcers. Other therapies with potential for treating IBD associated with anemia include treatment with anti-IL-6, which is the major inflammation-driven inducer of hepcidin, and other new therapies that neutralize hepcidin, modify EPO and/or erythropoietin receptor sensitivity, or affect cytokines to effectively stimulate erythropoiesis.

The multi-factorial origin of anemia in IBD implies that several leading mechanisms can be simultaneously identified in a single patient, including chronic intestinal blood loss, decreased absorption capabilities of the small bowel secondary to inflammation or resection, bacterial overgrowth, and an inability of many IBD patients to tolerate the side effects of oral ferrous sulfate, among others[108]. Each of these causative factors usually requires a specific therapeutic approach. Disease inflammatory activity and iron deficiency should be the first aspects to be restored in every patient[109] since they are the main causes of anemia and easily identified. Although more uncommon, vitamin B12 or folate deficiency, hemolytic and drug-induced anemia should also be born in mind. Effective treatment is only possible if the con-

tributing factors in a particular patient are clearly defined and corrected[110].

CONCLUSION

Anemia is a common multifactorial complication in IBD that increases disease morbidity. Awareness on the part of gastroenterologists needs to be increased to improve the specific diagnosis and management of anemia in these patients. New generation Ⅳ iron compounds are currently available to treat iron deficiency effectively in IBD patients. Further studies are needed to establish standardized treatments to reduce the development and recurrence of anemia as well as to improve the clinical course of IBD.

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