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TOPIC HIGHLIGHT

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Anemia and inflammatory bowel diseases

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Abstract

Too often anemia is considered a rare or unimportant manifestation in inflammatory bowel disease (IBD). However, over the last 10 years a number of studies have been conducted and the most relevant conclusions obtained are: (1) anemia is quite common in IBD; (2) although in many cases anemia parallels the clinical activity of the disease, many patients in remission have anemia, and iron, vitamin B12 and/or folic acid deficiency; (3) anemia, and also iron deficiency without anemia, have important consequences in the clinical status and quality of life of the patient; (4) oral iron can lead to gastrointestinal intolerance and failure of treatment; (5) intravenous iron is an effective and safe way to treat iron deficiency; (6) erythropoietin is needed in a significant number of cases to achieve normal hemoglobin levels. Thus, the clinician caring for IBD patients should have a comprehensive knowledge of anemia, and apply recently published guidelines in clinical practice.

Key words: Anemia; Inflammatory bowel diseases; Ferritin; Iron

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INTRODUCTION

In addition to the intestinal signs and symptoms (such as abdominal pain or diarrhea), inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are associated with a number of extraintestinal manifestations (at joints, skin, eyes, *etc*). Furthermore, systemic manifestations of IBD may also include malnutrition and anemia[1,2].

Compared with the average awareness of other extraintestinal disease complications such as arthritis or osteopathy, the topic of anemia in IBD has received little attention: perhaps it is so common that sometimes it is considered an unavoidable manifestation of the disease[2,3]. Although efficient therapeutic options have been developed for the treatment of IBD-associated anemia, treating anemia often has had a low priority for gastroenterologists[4]. However, anemia is a clinically relevant condition which may affect quality of life or the ability to work[5,6], and it is a comorbid condition which is associated with other diseases (such as transfusion-associated hepatitis C) or even death[1,7].

Anemia is a disease and should be approached as such. Anemia in IBD is not just a laboratory marker, it is a condition which needs a specific diagnostic and therapeutic approach. Moreover, it is a complex condition, because there are many factors which can cause anemia in IBD patients.

The aim of the present manuscript is to review the main clinically relevant aspects of the diagnosis and management of anemia in the patient with IBD.

PREVALENCE OF ANEMIA IN IBD

Often anemia is not even mentioned, perhaps because some authors think it is a rather uncommon problem in IBD[2]. On the contrary, anemia is very common in IBD patients, although the reported prevalence of this condition has been markedly variable, depending both on the definition and on the patient population considered (hospitalized patients *vs* outpatients)[1,8]. In a systematic review published in 2004, the prevalence of anemia in

patients with IBD ranged from 9% to 74%[8]. In a more recent systematic review[1], which included 19 studies (mainly on Crohn's disease) the figures ranged from 6% to 74%. Even more recently, we reviewed published studies evaluating the prevalence of anemia in IBD[9-30], and calculated a mean prevalence of 17%[2]. However, as the prevalence was 16% in outpatients, this figure increased up to 68% when only hospitalized patients were included. Therefore, it may be concluded that anemia could be the most common systemic complication of acute IBD[2].

PREVALENCE OF IRON DEFICIENCY IN IBD

It is also common to consider that iron deficiency is an exceptional finding in IBD[2]. On the contrary, this condition is even more common than anemia, but to demonstrate it requires active investigation. In fact, iron deficiency is the main cause of anemia in IBD patients, as a consequence of dietary restrictions, malabsorption (in part as a result of inflammation), intestinal bleeding, and/or undertreatment of anemia (achieving normal hemoglobin values does not mean normal iron stores). In a recent systematic review[1], the prevalence of iron deficiency ranged from 36% to 90% (depending on the definition of iron deficiency and on the type of cohort included)[16,21,26,31-33]. In the most recent systematic review[2], mean prevalence of iron deficiency in IBD was 45%, which underlines the fact that this condition may be considered the rule rather than the exception in these patients, especially in severe cases.

THE MULTIFACTORIAL ORIGIN OF ANEMIA IN IBD

Anemia in patients with IBD results primarily from iron deficiency because of chronic intestinal blood loss from inflamed mucosa, although in active disease more complex mechanisms involving absorption are also important[34]. However, the anemia in IBD is likely to be multifactorial in origin, frequently being the result of a combination of iron deficiency (the first cause) and anemia of chronic disease (the second major cause)[35]. In some cases, anemia may also be induced by drugs (sulfasalazine, thiopurines), hemolysis, and myelodysplastic syndrome. Finally, in some patients with Crohn's disease, impaired absorption of vitamin B12 and/or folate because of small intestinal inflammation and/or extensive bowel resection, may contribute to anemia[35], and all these conditions frequently overlap. Therefore, anemia in IBD is often complex and commonly represents a particular example of the combination of, at least, iron deficiency anemia and anemia of chronic disease, and may be a challenge even to the most astute clinician[4,24].

IRON METABOLISM PARAMETERS FOR THE DIAGNOSIS OF IRON DEFICIENCY IN IBD

The diagnosis of iron deficiency is traditionally based on a combination of parameters, including hematological and iron metabolism indices[36]. Pure iron deficiency is recognized by low iron, ferritin and transferrin saturation but increased transferrin concentrations. However, diagnosing iron deficiency in the setting of IBD may be difficult, particularly when both iron deficiency and the anemia of chronic disease are present (as previously mentioned, both conditions frequently coexist). In these circumstances, many of the laboratory measures of iron status may be unreliable, as inflammation influences parameters of iron metabolism[24,37]. For example, in the presence of chronic inflammation, the elevation in transferrin levels typical of iron deficiency may not be found, as patients with low albumin tend also to have low transferrin concentrations[38]. Similarly, iron and total iron binding capacity levels are often difficult to interpret in the presence of inflammation[35]. Finally, serum ferritin, the most accessible and well known measure of stored iron and the most powerful tests for iron deficiency[39], can be normal or even increased - in response to inflammation, as it is an acute phase reactant - even in the presence of severe iron deficiency[24]. Therefore, although at present ferritin is generally considered as the most efficient indicator of iron deficiency, this parameter may not provide adequate information about the storage compartment in the setting of inflammatory conditions such as IBD[24]. Testing for increased soluble transferrin receptor concentration distinguishes reliably between iron deficiency and anemia of chronic disease, but it is not yet widely available[40,41].

Accordingly, it has been suggested that diagnostic criteria for iron deficiency need to be adapted to the level of inflammation. Thus, in patients without biochemical (C-reactive protein, *etc*) or clinical (diarrhea, endoscopic findings, *etc*) evidence of inflammation, the cut-off point for defining a low level of serum ferritin is < 30 μg/L; however, in the presence of inflammation, the lower limit of this parameter consistent with normal iron stores should be increased up to 100 μg/L[37,42]. Some authors do suggest considering the presence of ferropenia if there are low iron values and < 16% transferrin saturation[43].

DRUG-RELATED ANEMIA IN IBD

Some drugs commonly used in the treatment of IBD can have myelosuppressive effects, both indirect (for instance the "antifolic" effect of salazopyrine) or even direct (such as azathioprine or mercaptopurine)[44]. In particular, sulfasalazine affects erythropoiesis by several mechanisms including folate absorption, hemolysis and aplasia[45]. Isolated anemia in patients on azathioprine or mercaptopurine is unlikely to be caused by these drugs; in some cases, however, a mild and asymptomatic reduction in hemoglobin may be detected in patients treated with thiopurine drugs.

THE IMPACT OF ANEMIA ON THE QUALITY OF LIFE OF IBD PATIENTS

The repercussion of anemia on quality of life in

both general patients[46,47] and specifically in patients with IBD[3,4,6,8] is substantial. Moreover, anemia may impair quality of life even in the absence of specific symptoms[5,6]. As has accurately been noted by Gasche *et al*[3,4], for a long time it was thought that the clinical symptoms of anemia (such as fatigue, headache, dizziness, shortness of breath, or tachycardia) occurred only when the hemoglobin level dropped abruptly. It had been argued that patients would adapt to low hemoglobin levels if anemia developed slowly. This has led to the concept of "asymptomatic" anemia. In truth, the term "asymptomatic" seems to reflect the fact that impairments in physical condition, quality of life, and cognitive function may be unrecognized by both patients and their doctors. Therefore, the process of adaptation to chronic anemia would, in fact, be adaptation to a lower quality of life[3,4]. These concepts have been thoroughly developed in other pathologies, especially in patients on dialysis: intravenous iron can be a key point in management of these patients[48].

Remarkably, the quality of life in IBD patients may be as low as in anemic patients with advanced cancer[49]. Moreover, chronic fatigue caused by anemia can debilitate, affect and worry these patients as much as abdominal pain or diarrhea[4]. Therefore the beneficial impact on quality of life derived from anemia correction in IBD patients can be similar to the control of diarrhea[4,6,50].

THE ROLE OF TREATMENT OF THE UNDERLYING DISEASE (IBD) ON THE CORRECTION OF ANEMIA

A general correlation exists between disease activity and the depth of the anemia[38]. Active disease can cause anemia because of multiple factors, the most recently demonstrated being anemia of chronic disease and impairment of iron absorption in active Crohn's disease. Therefore, the most important measure for IBD anemia treatment is the treatment of the underlying disease[1,24]. Although apparently obvious, sometimes this step is missed in actual clinical practice. Moreover, the long term effect to alleviate anemia depends on whether the bowel inflammation itself can be adequately treated. Every effort to accomplish this has to be undertaken in order to preclude recurrent anemia[37,51].

WHEN TO START IRON SUPPLEMENTATION IN IBD ANEMIC PATIENTS?

There may be a tendency to look upon anemia as an unavoidable accompaniment to IBD[38]. Only in recent years has correction of anemia been highlighted as a specific therapeutic aim in these patients[38]. It should not be assumed that some level of anemia is a normal finding in IBD patients and consequently need not be treated[3]. On the contrary, iron supplementation should be started as soon as anemia (hemoglobin < 13 g/dL in males, and < 12 g/dL in females[52]) is detected. Thus, the World Health Organization definitions of anemia apply to patients with IBD. In fact, it is possible that patients without anemia but with iron deficiency should be considered for treatment because even without anemia, iron deficiency can have clinical relevance. In summary, anemia in IBD patients should be aggressively diagnosed, investigated, and treated[2].

WHEN TO STOP IRON SUPPLEMENTATION IN IBD ANEMIC PATIENTS?

Apart from the correction of hemoglobin levels, the primary therapeutic goal is to improve quality of life. Therefore, the therapeutic objective of the treatment with oral iron should be to completely correct both the anemia and iron deficiency, and not only to partially increase the hemoglobin levels. Thus, our final aim should be to achieve the previously mentioned normal values (hemoglobin > 13 g/dL in males, and > 12 g/dL in females), in accord with that recommended in patients without IBD[3,4,53]. In fact, it is important to remember that the highest improvement in the quality of life is observed precisely when the hemoglobin levels increase from 11 to 13 g/dL[4,54]. Moreover, all patients should receive enough iron supplementation to correct anemia and replenish body stores[39,55]. In other words, the goals of anemia treatment, both in patients with and without IBD, are to normalize not only the hemoglobin value but also the iron stores, usually defined by the serum ferritin level[2].

DOSE OF IRON SUPPLEMENTATION IN IBD ANEMIC PATIENTS

Although conventional wisdom "says" that up to 200 mg of elemental iron (and even 400 mg in some textbooks) per day is required to correct iron deficiency anemia, this is probably incorrect[56]. Since a maximum of 10-20 mg of oral iron can be absorbed per day, very high doses and even high doses are questionable. In fact, there is no rationale to use "high" doses of iron to treat iron deficiency anemia (in IBD or in any other associated disease). There is no evidence to support high doses of iron in comparative trials[57-59]. This makes sense from a physiologic standpoint since it is well known that the iron absorptive process is very efficient yet can be saturated[56]. In this respect, a single tablet of most of the ferrous salt preparations (for example sulphate) provides more iron than the intestine is able to absorb in one day[57,58]. On the other hand, non-absorbed iron salts can be toxic to the intestinal mucosa[60-67], and perhaps could activate the disease[1,24]. In any case, high doses of iron may cause diarrhea, which in turn not only impair quality of life but also may make it difficult to differentiate from an IBD relapse[65,68]. Finally, non-absorbed iron salts may inhibit (i.e. by feedback) the intestinal iron absorption and decrease tolerance and compliance, which is difficult especially in young patients requiring several complex oral treatments.

Therefore, since absorption and efficacy of oral iron are no greater when high doses are used, and because adverse effects of this preparation are dose-related, oral iron, if used, should be recommended in low doses (e.g. 50-100 mg of elemental iron daily)[2].

RESPONSE OF ANEMIA TO ORAL IRON SUPPLEMENTATION IN IBD PATIENTS

The main factor in favor of oral iron is convenience. However, even when iron treatment is correctly prescribed, the oral route has relevant limitations, such as[2]: (1) only part of the iron is absorbed and, as previously mentioned, experimental and clinical evidence suggests that the non-absorbed iron salts can be toxic and proinflammatory, and perhaps could activate the disease[1,24]; (2) absorption of oral iron can be severely compromised because of disease activity[34], and in some Crohn's disease cases because of previous intestinal resections or involvement of the duodenum; (3) oral iron is often not well tolerated by patients. From a recent systematic review on the management of anemia in IBD which included several studies prescribing oral iron[27,35,65-67,69,70], the intolerance rate (mainly because of nausea, abdominal pain, or diarrhea) was a common finding leading to discontinuation in up to 21% of the cases[1]. Moreover, IBD patients often do need to take several oral drugs and overall compliance could be compromised by oral iron side effects[71]; (4) oral supplementation results in a slow response, and in some patients persistent blood loss exceeds the capacity of intestinal absorption of iron[72].

INTRAVENOUS IRON FOR THE TREATMENT OF IRON DEFICIENCY ANEMIA IN IBD

The efficacy of intravenous iron for the treatment of iron deficiency anemia in the general population (without IBD) has been demonstrated in numerous studies[73]. Although the experience with intravenous iron in IBD is more limited, it is similarly encouraging[6,16,50,51,66,70,74-78]. Iron sucrose was prescribed in most cases, which was effective in 50%-91% of the patients (depending on the criteria used for efficacy definition)[1]. More recently, a mean response of iron deficiency anemia to the treatment with this intravenous iron formulation was calculated to be 73%, which is a considerably high figure[2]. In summary, intravenous iron sucrose is more effective (in terms of faster and prolonged response) than oral iron supplements, and has a better safety profile which might positively influence the compliance of IBD patients. Accordingly, the inconvenience of intravenous iron is offset by the advantages in achieving better therapeutic results.

Following a widely recommended algorithm, the initial therapeutic strategy of iron deficiency anemia in IBD patients would be based on the level of hemoglobin. Patients with hemoglobin > 10/10.5 g/dL would initiate treatment with oral iron, while in those with levels < 10/10.5 g/dL, which are generally considered to denote severe anemia, the intravenous route would be of choice[1,3,8]. Intravenous iron should also be prescribed to patients with hemoglobin > 10/10.5 g/dL when intolerance to the oral formulation is present. In summary, the established indications for the use of intravenous iron are: severe anemia (generally defined as hemoglobin < 10 g/dL[1,8,37], although some authors set the cut-off point at 10.5 g/dL), need for quick recovery in mild anemia, intolerance to oral iron, and failure of oral iron.

Although in IBD iron sucrose is the most used intravenous formulation; there are other new intravenous iron preparations which theoretically could be used, with an extremely low incidence of adverse effects, and in particular severe adverse effects[1,73,79,80], but data in the specific IBD population is lacking, as reviewed by Auerbach[79]. The experience with low-molecular-weight iron dextran is rather more extensive and encouraging[79] and also a new molecule, iron carboxymaltose, merits mention because its pharmacokinetic characteristics and preliminary clinical experience seems very promising, and in this case was obtained directly in an IBD population[81].

ROLE OF ERYTHROPOIETIN IN THE TREATMENT OF ANEMIA IN IBD

As previously mentioned, anemia in IBD patients results primarily from iron deficiency because of chronic intestinal blood loss. However, intestinal inflammation is mediated by overproduction of cytokines, which may contribute to the generation of anemia in chronic disease, accompanied by inadequate erythropoietin production[16]. Thus, IBD-associated anemia is a unique example of a combination of chronic iron deficiency and anemia of chronic diseases. Since it was first used in chronic renal failure, recombinant human erythropoietin has been shown to be effective for treating the anemia that accompanies several chronic diseases[41]. During the last few years, several studies have evaluated the efficacy of erythropoietin in IBD patients, reporting encouraging results[16,20,27,50,75,82-84]. Nevertheless, as the cost of erythropoietin is much higher than the cost of intravenous iron, the latter formulation should be considered first-line therapy in patients with severe anemia, and erythropoietin therapy should be considered only for patients with low erythropoietin levels or who are unresponsive to intravenous iron[37,85]. One must not forget to exclude or correct other causes of anemia in IBD patients before administering erythropoietin[86]. Finally, erythropoietin should be reserved for patients in which aggressive management of IBD (including immunosuppressive therapy) has not suppressed inflammation, which underlines the idea that erythropoietin is an adjunct, - and not an alternative, -to appropriate treatment of IBD[38].

Erythropoietic agents should always be combined with intravenous iron supplementation, because functional iron deficiency, -defined as an inappropriate availability of iron for erythropoiesis despite normal

body iron stores, is likely to develop[76]. In the particular case of Crohn's disease, folic acid and vitamin B12 status should also be frequently checked[43] and deficiencies adequately corrected. Accordingly, erythropoietin therapy has been accompanied by iron supplementation in all trials published so far[1]. In summary, the enhancement of erythropoiesis by erythropoietin makes it mandatory to administer iron supplementation during therapy to meet the increased demand[86].

CONCLUSION

Anemia is rather common in IBD. Particularly in Crohn's disease, it can be a very difficult clinical problem because iron deficiency, vitamin B12 and/or folic acid defects, malabsorption, malnutrition, inflammation, intestinal resection, and drug effects all can be the cause or contribute to a multifactorial and complex problem. The control of inflammation is a key point, but often is not enough to treat anemia. As anemia has a considerable impact on the quality of life of patients, a thorough and complete diagnostic and therapeutic strategy should be followed to help our patients have as normal a life as possible. Very recent evidence raises a very important problem for the clinician: anemia can be a chronic or at least a recurrent problem in IBD; patients should be followed up after completing treatment, and anemia and iron deficiency actively assessed in the standard investigations[48].

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