

Management of anemia in inflammatory bowel disease: a challenge in everyday clinical practice

Edyta Tulewicz-Marti¹, Andrzej Moniuszko¹, Grażyna Rydzewska^{1,2}

¹Department of General Medicine and Gastroenterology with Inflammatory Bowel Disease Subdivision, Central Clinical Hospital of the Ministry of Interior Affairs and Administration, Warsaw, Poland

²Faculty of Medicine and Health Sciences, Jan Kochanowski University, Kielce, Poland

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Address for correspondence: Edyta Tulewicz-Marti MD, Department of General Medicine and Gastroenterology with Inflammatory Bowel Disease Subdivision, Central Clinical Hospital of the Ministry of Interior Affairs and Administration, 137 Woloska St, 02-507 Warsaw, Poland, phone: +48 22 508 12 40, fax: +48 22 508 10 40, e-mail: e.tulewicz@gmail.com

Abstract

Anemia is the most common extraintestinal manifestation and complication of inflammatory bowel disease (IBD). Its etiology is multifactorial and mostly is a combination of iron deficiency anemia (IDA) and chronic anemia (ACD). Because of its high incidence in patients with IBD and its influence on their quality of life, regular screening is recommended. In case of IDA type of medication and route of administration should be determined by many factors such as general condition of the patient, IBD activity or anemia severity. Intravenous iron supplementation is the preferred route but may be associated with phosphate drop or even severe hypophosphatemia (HP). The mechanism of HP related to the intravenous iron infusions is not clearly known yet, but it might be related to the change of FGF-23 levels. What more not all parenteral forms of iron are equal and some may have a higher risk of HP than others.

Introduction

Inflammatory bowel disease (IBD), encompassing Crohn's disease (CD) and ulcerative colitis (CU), is a chronic gastrointestinal disease characterized by a history of exacerbations and remissions and a multifactorial, not fully understood etiology. It is probably influenced by a genetic predisposition, the enteric microflora and environmental factors. The most common symptoms of IBD are related to chronic inflammation of the digestive system such as diarrhea and abdominal pain. They may be accompanied by different extraintestinal manifestations which involve the musculoskeletal (e.g. arthritis), dermatologic (e.g. erythema nodosum or pyoderma gangrenosum), and hepatopancreatobiliary system (e.g. primary sclerosing cholangitis) or ocular lesions (e.g. uveitis). The most common extraintestinal manifestation and complication of IBD is anemia [1], which affects up to 74% of patients [2, 3]. According to the ECCO-EpiCom study it affects approximately 42% during the first year from diagnosis [4]. In most cases, it is a combination of iron deficiency anemia (IDA) and

chronic anemia (ACD). Other causes include vitamin B₁₂ and folate deficiency or the toxic effect of medications. Anemia is not just a laboratory parameter but is a serious medical condition significantly affecting the quality of life [5, 6] and work of IBD patients [7], which also increases hospitalizations and generates additional health care costs.

Diagnosis and prevalence of anemia in inflammatory bowel disease

According to the 1968 definition by the World Health Organization, still used today, anemia is a condition in which the number of red blood cells or their oxygen-carrying capacity is insufficient to meet physiologic needs, which vary by age, sex, altitude, smoking, and pregnancy status [8]. The overall anemia cut-offs, presented in Table I, also apply to IBD patients and should be an aim of the iron supplementation. African Americans have lower limits of hemoglobin – 11.5 g/dl for women and 12.9 g/dl for men.

At the time of diagnosis, about 40% of adult patients have anemia. In the pediatric population these

Table I. Hemoglobin levels to diagnose anemia at sea level

Population	Hg [g/dl]	Ht (%)
Children 6–59 months of age	11	33
Children 5–11 years of age	11.5	34
Children > 12 years of age	12	36
Pregnant women	11	33
Non-pregnant women	12	36
Men (15 years and above)	13	39

figures are higher and may be 75% [9, 10], while iron deficiency can be up to 85% [11]. In the Swedish IBSEN study (a 10-year follow-up of more than 700 patients with IBD), anemia was more common in patients with CD than CU and was more common in women with CD after 10 years of treatment [12].

Because of the high incidence of anemia in patients with IBD and its influence on quality of life, regular screening of patients is recommended. In accordance with ECCO recommendations (1B) [13] and recommendations of the Polish National Consultant in Gastroenterology, regular follow-ups of patients in remission should be performed every 6–12 months, and of patients with active disease every 3 months [14, 15]. For laboratory screening, full blood count, C-reactive protein (CRP), and serum ferritin should be used. In patients at risk of vitamin B₁₂ and folate deficiency or in case of macrocytosis in absence of therapy with thiopurines, the level of B₁₂ and folate should be measured at least annually.

Anemia work-up

The initial work-up of anemia should start with evaluation of mean corpuscular volume (MCV), helping to distinguish between different etiologies: microcytosis such as IDA, macrocytosis (vitamin B₁₂ and folate deficiency or thiopurine treatment) or normocytosis (ACD). Secondly, reticulocyte count should be evaluated in order to assess the ability of bone marrow to respond properly to anemia. Low or normal reticulocyte count may indicate inappropriate erythropoiesis or primary bone marrow disease, while increased reticulocytes indicate correct red cell formation. Moreover, normal platelet and white blood cells count exclude pancytopenia. Incorrect haptoglobin, lactate dehydrogenase and bilirubin levels may indicate hemolysis.

Iron deficiency anemia

Iron is an essential substrate in cellular metabolism and overall organism functioning, including transport

of oxygen, energy production and cell proliferation [15]. Patients suffering from iron deficiency may complain about fatigue, tiredness, decreased concentration and eventually anemia. Iron deficiency without anemia may be manifested by weakness, sleep disorders, restless legs syndrome, attention deficit or infertility in women [16–18]. In patients with IBD, iron deficiency anemia and anemia of chronic disease often overlap and knowing its etiology is crucial for correct management.

Iron deficiency may be caused by malnutrition with poor oral supply of the element, impaired iron absorption or chronic bleeding from the intestinal mucosal ulcers. The IDA diagnostic criteria vary depending on whether the patient is in remission or in the active phase of the disease. Therefore, in patients without endoscopic, biochemical and clinical features of disease exacerbation, low ferritin levels ≤ 30 $\mu\text{g/l}$ indicate iron deficiency, while in case of exacerbation the cut-off is higher – 100 $\mu\text{g/l}$. On the other hand, serum soluble transferrin receptor (sTfR) concentrations are independent from the inflammatory state and are indicators of overall iron metabolism. It is very important to screen for anemia knowing that parenteral iron supplementation seems to increase the patient's quality of life in the case of both anemic and non-anemic iron deficiency.

Anemia of chronic diseases

Anemia of chronic diseases is associated with and caused by a chronic inflammatory state. In case of active inflammation, there is an increase in the production of cytokines that stimulate the production of hepcidin in the liver. It decreases iron exports from macrophages to the endoplasmic reticulum by reduction of ferroportin. Therefore there is a reduction of transferrin saturation and iron transport to the erythroblasts, creating functional iron deficiency (FID) for erythropoiesis [19]. In addition, high levels of hepcidin reduce the absorption of iron in the duodenum [20]. The described process can be observed in many medical conditions including IBD, cancer and rheumatic diseases. In presence of biochemical or/and clinical evidence of inflammation, ferritin levels above 100 $\mu\text{g/l}$ and transferrin saturation below 20% are diagnostic for ACD. Normal MCV does not preclude iron deficiency.

Management of iron deficiency anemia

Treatment of anemia should not be overlooked and should be started as soon as possible, as iron replacement improves quality of life of anemic and hypoferritemic patients with IBD [21]. The decision to initiate the therapy and route of administration depend on a number of factors including the general condition of the patient, IBD activity, anemia severity and the prior

tolerance of oral iron preparations. According to ECCO recommendations (2E) oral iron preparations may be used in patients in remission and with moderate anemia and in whom intolerance for oral iron (such as nausea, diarrhea, constipation and abdominal pain) preparations was not reported. Large amounts of iron in the intestinal lumen can cause oxidative stress and inflammation of the gut, leading to IBD exacerbation. Moreover, Zimmermann *et al.* observed that oral iron preparations may impair the gastrointestinal microbiome and increase fecal calprotectin [22]. For that reason, the maximum daily dose of basic iron in patients with IBD should not exceed 100 mg. According to the evaluation of prospective studies conducted by Nielsen *et al.*, parenteral formulations were more effective than oral treatments in relation to an increase in hemoglobin (Hb) levels in the case of severe anemia. In mild anemia higher ferritin without elevation of Hb was observed in patients who received iron *i.v.* [23].

Indications for parenteral iron supplementation are intolerance of oral iron preparations, severe anemia (Hb < 10 g/l) and need for erythropoiesis stimulants. It is not advisable to use intramuscular preparations because of many side effects, such as painful administration.

Patients with ACD and insufficient response to iron therapy should be considered for treatment with erythropoiesis. For severe anemia, blood transfusions followed by possible iron supplementation depending on hemoglobin levels should be considered.

Intravenous iron supplementation is the preferred route of iron supplementation in patients with IBD. The following preparations are available on the Polish pharmaceutical market: iron (III)-hydroxide dextran complex (Cosmofer), iron (III) isomaltoside (ISM) (Monover), iron sucrose (Venofer) and ferric carboxymaltose (FCM) (Ferinject). For the administration of dextran, the test dose is indicated. For the remaining drugs, only a 30-minute observation of the patient is indicated. In the past, to determine the correct iron dose as above, the Ganzoni formula [23] was used: total iron deficiency [mg] = body weight [kg] × (target hemoglobin – actual hemoglobin [g/dl]) × 0.24 + 500.

On the other hand, a simplified formula has been proposed. In the FERGIcor study, the previously used scheme and the new simplified scheme (Table II) of iron supplementation were compared. New scheme proved to be more practical and efficient than the complicated Ganzoni formula. The study was carried out for iron carboxymaltose. In the case of severe anemia (Hb 7 g/l) an additional dose of 500 mg *i.v.* iron is indicated [24].

To date, there are limited data comparing different parenteral iron preparations in the IBD population. Iron

isomaltoside can be administered with a maximum single dose of 20 mg/kg actual body weight, while ferric carboxymaltose can be administered with a maximum single dose of 1000 mg. A recent meta-analysis highlights that ferric carboxymaltose provides faster correction of Hb and serum ferritin levels in iron-deficient patients, with good tolerability of medication [25]. Iron isomaltoside appears to be less associated with hypophosphatemia than ferric carboxymaltose.

Prevention of iron deficiency anemia

Patients should be monitored every 3 months for 1 year and then every 6–12 months after receiving treatment. In case of decrease of ferritin under 100 µg/l, *i.v.* iron supplementation is indicated.

Treatment of anemia not caused by iron deficiency

The causes of anemia in IBD patients may vary, e.g. ACD, folic acid and vitamin B₁₂ deficiency, anemia induced by immunosuppressants or bone marrow aplasia. Their treatment depends on the cause of anemia.

Hypophosphatemia related to parenteral iron infusion

Parenteral iron preparations are considered as safe but still may lead to hypophosphatemia and hypersensitivity reactions. Iron-induced hypophosphatemia was reported for the first time in 1982 as a complication of repeated *i.v.* therapy with saccharated iron oxide [26]. According to the 2008 FDA report, 2.1% of patients treated with intravenous carboxymaltose developed hypophosphatemia. Hardy and Vandemergel reported a high prevalence of severe hypophosphatemia (32.1%) after treatment of iron deficiency with high-dose intravenous ferric carboxymaltose in patients with gastrointestinal disorders [27]. According to the study of Bager *et al.* which compared the effects of ferric carboxymaltose and iron isomaltoside, hypophosphatemia occurred more often in patients who received FCM than the latter drug (up to 50% vs less than 10% of patients), which confirmed the previous data [28].

Phosphate plays a crucial role in homeostasis and takes part in many biological processes. It is a key mol-

Table II. Dosage of iron according to patient's weight

Hemoglobin [g/dl]	Body weight < 70 kg [mg]	Body weight > 70 kg [mg]
10–12 women 10–13 men	1000	1500
7–10	1500	2000

ecule for nucleic acid synthesis, intracellular signaling and bone formation. In healthy subjects, phosphate is obtained primarily from the diet and its metabolism is regulated by factors such as parathyroid hormone and vitamin D. The mechanism of hypophosphatemia occurring after the administration of different parenteral iron is not yet fully understood, but it is probably related to increased secretion of fibroblast growth factor 23 (FGF23). The peptide binds the FGF receptor on target cells along with such cofactors as the protein Klotho and downregulates proximal renal tubule phosphate co-transporters. It induces phosphaturia and suppresses levels of 1,25-dihydroxyvitamin D. Recent data suggest that iron deficiency may stimulate FGF23 transcription in osteocytes [29]. According to a study of Wolf *et al.* on the effect of a single dose of FCM or iron dextran on intact, active hormone FGF23 (iFGF23) and biologically inactive, C-terminal FGF23 (cFGF23) levels in iron-deficient, anemic women, iron deficiency anemia was associated with markedly increased cFGF23 levels and normal iFGF23. Moreover, ferric carboxymaltose caused an increase of iFGF levels and subsequently decreased serum phosphate, 1,25-dihydroxyvitamin D and calcium levels, followed by the increase of PTH. This cascade was accentuated in those individuals who experienced the greatest phosphate decrease.

The lowest HP occurs 1–2 weeks after iron administration [30] and the median time of normalization after a single iron infusion is 84 days, but may be prolonged after repetitive *i.v.* iron infusions.

There are known cases of symptomatic hypophosphatemia following intravenous iron administration such as fatigue or muscle weakness, and even osteomalacia or secondary bone fractures for long-term parenteral iron supplementation [31, 32]. Symptomatic hypophosphatemia is more commonly associated with chronic iron use, low levels of ferritin and gastrointestinal disorders and malnutrition. The management of drug-induced symptomatic hypophosphatemia involves immediate discontinuation of intravenous iron treatment, together with phosphorus oral supplementation and dietary calcium restriction. Vitamin D deficiency should be screened and supplemented in case of deficiency, as it may help to increase phosphate intestinal absorption, even though calcitriol cannot correct FGF23 excess. Calcium and phosphorus levels should also be monitored in symptomatic patients. Treatment should be applied on the day of iron administration and on a daily basis for 3–4 weeks.

Conclusions

The most common cause of anemia in IBD is multifactorial – iron deficiency, chronic anemia, drug ef-

fects or deficiency of vitamin B₁₂ and folic acid. It is important to screen and treat it accordingly. Intravenous preparations of iron are capable of delivering a high dosage of iron in a single or low number of visits, increasing the patient's quality of life. Even though *i.v.* iron has minimal potential effects, physicians should be aware of side effects which they may cause such as hypophosphatemia. Frequent check-ups should be carried out.

Conflict of interest

The authors declare no conflict of interest.

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