

Iron deficiency anaemia in patients with inflammatory bowel disease: National Consultant for Gastroenterology Working Group Recommendations

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Abstract

Anaemia is a common complication associated with inflammatory bowel diseases (Crohn's disease and ulcerative colitis). It substantially impairs quality of life, makes therapy more complicated, and increases costs of treatment. It seems that anaemia therapy is suboptimal in this group of patients in the Polish population. The recommendations presented below provide iron deficiency anaemia management clues in patients with inflammatory bowel disease.

Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic gastrointestinal illnesses of multifactorial aetiology, which proceed with periods of relapse and remission. These conditions are often associated with extraintestinal manifestations or complications, and iron deficiency anaemia is foremost among them. The pathomechanism of anaemia in IBD patients is multifactorial, but iron deficiency seems to be the most important cause. Anaemia significantly impairs quality of life and modifies host

immunological status and morbidity, especially in terms of concomitant infections; it also appears to be a mortality-increasing factor [1–3]. Iron deficiency anaemia management in IBD patients continues to be suboptimal in Poland, and reports presented at European Crohn's and Colitis Organisation (ECCO) meetings suggest blood transfusions are used too freely in this group of patients.

The panel of invited experts reached a consensus in terms of defining the most important concepts of anaemia in IBD, and they discussed optimal diagnostic and therapeutic strategy.

Diagnosis

Regarding its significant impact on quality of life and mortality, every IBD patient should be tested for anaemia. If haemoglobin levels below lower limit of normal are found, diagnostic workup commencement is of utmost importance.

Comments

The World Health Organisation defined the lower limit of normal for haemoglobin and haematocrit according to age and sex [2, 3] (Table I).

There is no need to establish a new definition of anaemia in IBD, so in this patient group standard criteria are adopted regarding age, sex, and potential pregnancy [1].

Biochemical tests

Inflammatory bowel diseases patients should have haemoglobin, ferritin, and C-reactive protein (CRP) measured at least every 6 to 12 months when in remission or with mild disease, and every 3 months when moderate to severe relapse occurs.

Patients at high risk of vitamin B₁₂ or folic acid deficiency (particularly with small intestinal involvement or resection, as well as ileal pouch) should have vitamin B₁₂ and folic acid levels assessed at least yearly, especially when macrocytosis is detected.

Once low haemoglobin is detected, at least ferritin, transferrin saturation (TfS), and CRP measurement is recommended.

Table I. Haemoglobin (HGB) and haematocrit (Ht) lower limit of normal, according to the WHO [3]

Group	HGB [g/dl]	HGB [mmol/l]	Ht [%]
Children 6 months – 5 years	11	6.83	33
Children 5–11 years	11.5	7.14	34
Children > 12 years	12	7.45	36
Pregnant women	11	6.83	33
Adult females	12	7.45	36
Adult males	13	8.07	39

Comments

In differentiation of the most frequent types of anaemia, such as iron deficiency anaemia (IDA) and anaemia in chronic disease (ACD), the algorithm presented in Table II can be used [4–6]. It is particularly important in IBD patients because both types of anaemia commonly coexist; moreover, active inflammation (based on CRP assessment) alters interpretation of other laboratory results.

Iron deficiency anaemia

Ferritin is the best single diagnostic parameter in iron deficiency anaemia detection.

Comments

Ferritin measurement is much more useful than the other parameters discussed earlier. However, it must be kept in mind that ferritin is an acute phase protein so test results have to be interpreted in correlation with the disease activity. Iron deficiency in patients with absent biochemical inflammatory markers is reflected by ferritin levels < 30 µg/l (TfS < 16%). In active inflammatory process, ferritin levels may be as low as 100 µg/l when iron stores are normal and > 800 µg/l if iron overload has occurred [1, 7]. Iron deficiency in IBD may have various backgrounds based on disease phase, previous surgery, malabsorption, or, above all, increased losses associated with active inflammation.

Independent of diminished iron levels anaemia assessment should include:

- potential comorbidity (malignancy, infection),
- treatment side effects (thiopurine, methotrexate, sulphasalazine).

In chronic disease-related anaemia with clinical symptoms or biochemical markers of inflammation,

Table II. Differential diagnosis of iron deficiency anaemia (IDA) and anaemia in chronic inflammatory disease (ACD)

Laboratory parameter	IDA	ACD	IDA + ACD
Haemoglobin	↓	↓	↓
C-reactive protein (CRP)	Normal	↑	↑
Serum ferritin	↓	↑	↑ or normal
Transferrin saturation (TfS)	↓	↓	↓
Soluble transferrin receptor (sTfR)	↑	Low (< 1)	↑ or normal

diagnostic criteria are as follows: ferritin > 100 µg/l and TfS < 16%. If ferritin levels are between 30 µg/l and 100 µg/l, the coexistence of iron deficiency anaemia and anaemia in chronic disease seems to be most likely [6].

Treatment

In IBD patients with associated anaemia the aim of treatment strategy is normalisation of haemoglobin and iron levels. Ferritin and transferrin saturation increase above borderline values should be considered as well.

Comments

The aim of anaemia therapy in IBD is to improve quality of life, decrease the frequency and duration of hospital admissions, and avoid blood transfusions. It is usually achieved by normalising haemoglobin, ferritin, and TfS levels.

Anaemia management should be considered in every patient with low haemoglobin level. The decision about pharmacotherapy depends on anaemia degree, symptoms, and potential drug side effects. Quality of life decrease without clinical symptoms or signs of anaemia and with merely low laboratory parameters such as transferrin saturation, ferritin, or iron levels has to be taken into account [4]. When iron deficiency with borderline haemoglobin concentration is detected, iron supplementation should be considered and discussed with the patient.

Before iron deficiency anaemia management is commenced it should be born in mind that oral iron can enhance gastrointestinal inflammatory process by toxic mucosal damage induction, which is caused by hydroxyl free radicals generated during iron oxidation triggered by hydrogen peroxide (Fenton reaction) [8, 9]. In addition, oral iron is often poorly tolerated in this group of patients. Regarding better effectiveness and tolerability, intravenous iron is preferred in IBD patients. In particular, intravenous iron formulation is recommended in severe IBD when oral supplementation is ineffective or poorly tolerated (in 20% of IBD patients), when haemoglobin is < 10 g/dl, or during erythropoietin administration [10].

Iron deficiency assessment

For iron deficiency assessment the Ganzoni formula is commonly used: iron deficit [mg] = body weight [kg] × (target haemoglobin – actual haemoglobin) [g/l] × 0.24 + 500 mg. In patients with less than 35 kg body weight, an iron dose of 15 mg/kg is suggested.

Table III. Iron dosage based on baseline patient haemoglobin (HGB) and body weight

HGB [g/dl]	Body weight < 70 kg	Body weight > 70 kg
> 10	1000 mg	1500 mg
7–10	1500 mg	2000 mg

Comments

In most previous reports iron deficiency was established using the Ganzoni formula [11]. However, it seems that iron deficit calculated using this method does not reflect real iron requirements.

Among others, it was demonstrated in a Ferinject trial in which only 26.5% of patients receiving full iron dose calculated on the Ganzoni formula basis were able to reach the desired ferritin level (100–800 µg/l) at the end of it [12]. Recently an alternative iron dosage scheme based on baseline patient haemoglobin and body weight was used in the FERGLcor trial [13] and in the PROCEED trial [14] (Table III).

In the two above-mentioned trials the efficacy and safety of intravenous iron compounds were assessed, as well as a new and simplified dosing scheme for Monover and Ferinject, and the Ganzoni formula for Venofer. Patients treated with Ferinject received approximately 200 mg overall extra dose of iron as compared with Venofer patients. Although significant haemoglobin increase was achieved in 73% of patients, recommended ferritin elevation > 100 µg/l was reported in 31% of patients only [13]. Monover administered in a single dose ranging from 1000 mg to 2000 mg allowed ferritin, haemoglobin, and TfS levels to be kept stable over a 12-month period [14]. It would seem that iron requirement calculations based on general rules do not always prove correct in IBD patients.

The Working Group encourages physicians to familiarise themselves with a tool called a Ferroscope, created to facilitate therapeutic decision making in IBD patients with iron deficiency [15]. It includes several thousand scenarios involving sex, haemoglobin and ferritin levels, disease activity, previous iron deficiency treatment, clinical symptoms of anaemia, or additional factors increasing the need for iron. When data is introduced into the system it is possible to gain clues regarding optimal patient management. Therapeutic options labelled as appropriate, uncertain, and inappropriate include iron administration orally, intravenously in low doses (< 500 mg per single dose) or high doses (≥ 500 mg per single dose), the addition of erythropoiesis stimulating drugs, or blood transfusion. The free catalogue is available online at: www.ferroscope.com.

During treatment it is advisable to aim at gaining haemoglobin elevation by 2 g/l or its normalisation within 4 weeks of therapy [4]. If sufficient therapeutic effect is lacking, treatment intensification (oral to intravenous shift, intravenous formulation usage allowing high single dose administration, or erythropoiesis stimulating factor addition) or other coexisting anaemia cause exclusion should be considered. Regarding the appropriateness of iron deficit replacement within a 4-week treatment period, administration of higher single doses of iron seems beneficial as a therapeutic option in patients with severe anaemia [4, 6, 15]. Asymptomatic patients should have haemoglobin measured after 4 weeks of treatment, whereas patients with previous symptoms of anaemia are usually tested on an individual basis, depending on the patient condition and baseline results. Ferritin elevation > 100 µg/l in patients on oral iron supplements is proof of treatment effectiveness. In patients treated intravenously, ferritin levels should be checked not earlier than 8 weeks post infusion [6].

Intravenous iron compounds

In Poland the following intravenous iron compounds are available: iron (III) – hydroxide sucrose complex (Venofer), iron (III) hydroxide low molecular weight dextran complex (Cosmofer), ferric isomaltose (Monover), and ferric carboxymaltose (Ferinject). Previously the administration of intravenous iron testing dose was obligatory, but currently it is not recommended. Close patient monitoring 30 min post every parenteral iron injection is advised.

Venofer may be administered three times a week until the calculated dose needed to replenish iron stores is reached. The maximal single dose of iron (500 mg; 7 mg/kg body weight) with infusion time approximately 3.5 h (4 mg/min) should not be exceeded. Commonly used doses are 200–300 mg infused in 100 ml or 250 ml 0.9% NaCl within 45–90 min.

Iron (III) hydroxide dextran complex (Cosmofer) is more stable and is slowly degraded, so it can be used in higher single doses. Recommended dosing is 100–200 mg of iron 2–3 times per week, although it is also accepted to infuse maximal dose of 20 mg/kg body weight during one drip infusion lasting 4–6 h.

Ferric isomaltose (Monover) is a safe drug, which does not need a testing dose and may be administered in high single doses. Intravenous 100–500 mg iron bolus injections given at a rate of up to 50 mg/min are recommended; doses of 100–200 mg can be repeated up to three times a week. A single high dose infusion can contain up to 20 mg of iron per kg body weight. The infusion velocity depends on the amount of iron

administered (doses not exceeding 1000 mg are given within 30 min, whereas higher doses are infused in 60 min time).

Ferric carboxymaltose (Ferinject), due to its pharmacokinetic properties, is a stable complex, as well as a safe and well tolerated iron compound. A single dose that can be administered safely during intravenous infusion lasting 15 min is 1000 mg (15 mg/kg body weight). Drug infusion can be repeated as required.

Erythropoietin therapy

Erythropoietin is indicated in IBD patients with anaemia related mainly to chronic inflammatory disease and in subjects with insufficient response to intravenous iron, in whom IBD therapy is optimal [4].

Comments

Erythropoietin administration should be considered in patients with haemoglobin less than 10 g/dl or in whom high dose intravenous iron therapy was unsuccessful (after 4 weeks of treatment). Such a therapy should be undertaken in patients with erythropoietin, sTfR, and TfS levels suggesting ineffectiveness of intravenous iron monotherapy [16].

Vitamin B₁₂ and folic acid deficiency anaemia treatment

In patients with identified vitamin B₁₂ or folic acid deficit, introduction of supplementation therapy is recommended.

Blood transfusion

Chronic gastrointestinal blood loss may occur in IBD patients. Repeated blood transfusions result in antibody formation, and as such their use should be limited to exceptional and emergency cases.

Comments

In every gastrointestinal bleeding associated with substantial haemoglobin drop, indication for blood transfusion should be assessed individually based on patient condition, age, comorbidities, and amount of blood lost. Blood transfusion does not replace intravenous iron therapy, which is sometimes applied in combination with erythropoietin. The patient should be monitored and further parenteral iron substitution scheduled post transfusion, even if haemoglobin level is normal [4].

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