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REVIEW ARTICLE

State of the iron: How to diagnose and efficiently treat iron deficiency anemia in inflammatory bowel disease

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Abstract

Iron deficiency anemia (IDA) frequently occurs in patients suffering from inflammatory bowel disease (IBD) and negatively impacts their quality of life. Nevertheless, the condition appears to be both under-diagnosed and undertreated. Regular biochemical screening of patients with IBD for anemia by the gastroenterology community has to be advocated.

Oral iron is a low cost treatment however its effectiveness is limited by low bioavailability and poor tolerability. Intravenous (IV) iron rapidly replenishes iron stores and has demonstrated its safe use in a number of studies in various therapeutic areas. A broad spectrum of new IV iron formulations is now becoming available offering improved tolerability and patient convenience by rapidly restoring the depleted iron status of patients with IBD. The following article aims to review the magnitude of the problem of IDA in IBD, suggest screening standards and highlight existing and future therapies.

Contents

Abbreviations: ACD, Anemia in chronic disease; CD, Crohn's disease; CDK, Chronic kidney disease; CHr, Reticulocyte hemoglobin content; ESA, Erythropoiesis stimulating agent; Hb, Hemoglobin; HMWID, High molecular weight iron dextran; IBD, Inflammatory bowel disease; ID, Iron deficiency; IDA, Iron deficiency anemia; IV, Intravenous; LMWID, Low molecular weight iron dextran; TDI, Total dose infusion; UC, Ulcerative colitis.

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1. Introduction

Anemia is a frequent extra-intestinal manifestation in inflammatory bowel disease (IBD) known to negatively impact physical quality of life.[1,2] Anemia has been even revealed as a co-morbid condition that contributes to death of patients with IBD.[3] Though it seems logical that anemia would also increase the rate of hospitalization and medical costs in IBD respective data are still lacking.

Iron deficiency (ID) and anemia of chronic diseases (ACD) are the most common causes of anemia in IBD. Therefore, together with an adequate control of underlying inflammation iron replacement therapy should start as soon as ID or anemia is detected to attain a normal iron status and Hb.[4] This results in improvement in the patients' quality of life independent of changes in disease activity.[1,5] Although efficient therapeutic options have been developed for the treatment of IBD-associated anemia, treating this manifestation appears to remain of low priority for gastroenterologists.[6,7]

This review aims to give some guidance on how to address ID in patients with IBD including screening procedures, therapeutic options and their potential outcomes. Furthermore the review discusses potential clinical benefits of a new generation of IV iron preparations in the treatment of IBD.

2. Prevalence and etiology of anemia in IBD

Prevalence rates of anemia in IBD are widely varying from 6 to 74%, which also appears to reflect differences in the standards of screening and treatment as well as in the settings under which patients were studied.[4] Anemia is reported more frequently in hospitalized patients with IBD and occurs more frequently in Crohn's disease (CD) as compared to ulcerative colitis (UC).[8,9] It also appears that hemoglobin concentrations increase in the years after diagnosis which may be explained by the remission of disease following successful medical or surgical treatment.[9]

Anemia in IBD is mainly the expression of a mixed pathogenesis with ID and ACD posing the most prominent factors often existing in parallel.[10] Nevertheless, with a reported prevalence of up to 90% ID is the most frequent cause.[4] Iron deficiency may be related to low dietary intake as well as low intestinal bioavailability of iron, decreased internal iron turn-over, and blood loss.[11,12] Semrin and co-workers suggested that inflammation may inhibit iron absorption as it correlates with disease activity and markers of inflammation in Crohn's disease.[13] The accurate contribution of intestinal blood loss as a source of ID has not been studied, although it is supposed to pose a major component.[9]

On the other hand, the exact prevalence of ACD is unknown.[14,15] The etiology of ACD is ascribed to altered erythropoiesis and red cell survival. IBD patients may suffer from functional iron deficiency (FID) due to iron retention in macrophages driven by pro-inflammatory cytokines and hepcidin. During an acute phase response hepcidin is induced in the liver by IL-6 and reduces iron absorption from the duodenum as well as iron recycling from macrophages.[16,17] In addition, chronic inflammation has been suggested to decrease erythropoiesis either directly by IFN-gamma or because of decrease in the synthesis and the biological activity of erythropoietin (EPO) induced by IL-1, IL-6, TNF-alpha, and hepcidin.[15,17]

Finally, it must be borne in mind that there are other frequent reasons for anemia in IBD patients. Vitamin B12 deficiency is commonly found in patients with IBD, particularly after resection of the ileum and may lead to hyperchromatosis and macrocytosis.[4,18,19] Prescribed medical treatment should also be considered as a potential cause of anemia in patients with IBD. Methotrexate and sulfasalazine interfere with the absorption of folate and may mediate folate deficiency.[18] Sulfasalazine may also induce hemolysis or bone marrow aplasia. Thiopurines and methotrexate can induce bone marrow toxicity in a minority of patients.[4]

3. Clinical manifestations and consequences of iron deficiency

Symptoms and signs of ID even without anemia comprise impaired physical performance, reduced cognitive function, fatigue, headache, dizziness, shortness of breath, restless legs syndrome, hair loss, angular stomatitis, glossitis, pica and reduced libido.[20] Other features include an increase in complications during pregnancy, blunted thermoregulation, and villous atrophy.[16]

IDA in addition has an impact on the immune status and morbidity from infections. ACD is caused by iron retention in macrophages. Phylogenetically this is an interesting and potentially protective innate immune function of the host because iron is a key growth and virulence factor for