Anemia and inflammatory bowel diseases

Fernando Gomollón, Javier P Gisbert

Fernando Gomollón, Gastroenterology Unit, Clinical Universitary Hospital “Lozano Blesa”, CIBEREHD, Avenida San Juan Bosco 15, Zaragoza 50009, Spain
Javier P Gisbert, Gastroenterology Unit, Universitary Hospital “La Princesa”, CIBEREHD, C/Diego de León 62, Madrid 28006, Spain

Author contributions: Gomollón F and Gisbert JP contributed equally to this work; Gisbert JP and Gomollón F performed the systematic review of the literature and wrote the paper.

Correspondence to: Fernando Gomollón, MD, PhD, Gastroenterology Unit, Clinical Universitary Hospital “Lozano Blesa”, CIBEREHD, Avenida San Juan Bosco 15, Zaragoza 50009, Spain. fgomollon@gmail.com
Telephone: +34-876-766000-2454 Fax: +34-976-768846
Received: July 23, 2009 Revised: August 12, 2009
Accepted: August 19, 2009
Published online: October 7, 2009

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.

© 2009 The WJG Press and Baishideng. All rights reserved.

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

Peer reviewer: Luis Rodrigo, Professor, Gastroenterology Service, Hospital Central de Asturias, c/Celestino Villamil, s.n., Oviedo 33.006, Spain

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. 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. 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). In a systematic review published in 2004, the prevalence of anemia in...
The diagnosis of iron deficiency is traditionally based on a combination of parameters, including hematological and iron metabolism indices. 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. 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. Similarly, iron and total iron binding capacity levels are often difficult to interpret in the presence of inflammation. Finally, serum ferritin, the most accessible and well known measure of stored iron and the most powerful tests for iron deficiency, 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. 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. Testing for increased soluble transferrin receptor concentration distinguishes reliably between iron deficiency and anemia of chronic disease, but it is not yet widely available.

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 \( \mu g/L \); however, in the presence of inflammation, the lower limit of this parameter consistent with normal iron stores should be increased up to 100 \( \mu g/L \). Some authors do suggest considering the presence of ferropenia if there are low iron values and < 16% transferrin saturation.

Some drugs commonly used in the treatment of IBD can have myelosuppressive effects, both indirect (for instance the “antifolic” effect of salazosalicylic acid) or even direct (such as azathioprine or mercaptopurine). In particular, sulfasalazine affects erythropoiesis by several mechanisms including folic acid absorption, folate synthase and aplasia. 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 repercussion of anemia on quality of life in patients with IBD ranging from 9% to 74%[8]. In a more recent systematic review, 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[8], the prevalence of iron deficiency ranged from 36% to 90% (depending on the definition of iron deficiency and on the type of cohort included)[2,26,28,31-33]. In the most recent systematic review[33], 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. 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)[3]. 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[30], 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[24].

IRON METABOLISM PARAMETERS FOR THE DIAGNOSIS OF IRON DEFICIENCY IN IBD
The diagnosis of iron deficiency is traditionally based on
both general patients and specifically in patients with IBD is substantial. Moreover, anemia may impair quality of life even in the absence of specific symptoms. As has accurately been noted by Gasche et al., 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. 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. Remarkably, the quality of life in IBD patients may be as low as in anemic patients with advanced cancer. Moreover, chronic fatigue caused by anemia can debilitate, affect and worry these patients as much as abdominal pain or diarrhea. Therefore the beneficial impact on quality of life derived from anemia correction in IBD patients can be similar to the control of diarrhea.

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. 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. 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.

WHEN TO START IRON SUPPLEMENTATION IN IBD ANEMIC PATIENTS?

There may be a tendency to look upon anemia as an unavoidable accompaniment to IBD. Only in recent years has correction of anemia been highlighted as a specific therapeutic aim in these patients. It should not be assumed that some level of anemia is a normal finding in IBD patients and consequently need not be treated. On the contrary, iron supplementation should be started as soon as anemia (hemoglobin < 13 g/dL in males, and < 12 g/dL in females) 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.

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. 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. Moreover, all patients should receive enough iron supplementation to correct anemia and replenish body stores. 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.

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. 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. This makes sense from a physiologic standpoint since it is well known that the iron absorptive process is very efficient yet can be saturated. 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. On the other hand, non-absorbed iron salts may be toxic to the intestinal mucosa, and perhaps could activate the disease. 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. 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)\[3\].

**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\[12,34\]; (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\[27,31,46-47,67-70\], 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\[71\]. 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\[27\].

**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\[16,20,27,50,75,82-84\]. Iron sucrose was prescribed in most cases, which was effective in 50%-91% of the patients (depending on the criteria used for efficacy definition)\[1,24\]. 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\[3\]. 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\[17,3,79,86\], 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\[16,20,27,50,73,82-84\]. 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\[87,88\]. 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. In the particular case of Crohn's disease, folic acid and vitamin B12 status should also be frequently checked and deficiencies adequately corrected. Accordingly, erythropoietin therapy has been accompanied by iron supplementation in all trials published so far. In summary, the enhancement of erythropoiesis by erythropoietin makes it mandatory to administer iron supplementation during therapy to meet the increased demand.

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.

REFERENCES

1. Kulnigg S, Gasche C. Systematic review: managing anemia in Crohn's disease. Aliment Pharmacol Ther 2006; 24: 1507-1523
2. de la Morena F, Gisbert JP. [Anemia and inflammatory bowel disease] Rev Esp Enferm Dig 2008; 100: 285-293
3. Gasche C. Anemia in IBD: the overlooked villain. Inflamm Bowel Dis 2000; 6: 140-152; discussion 151
4. Gasche C, Lomer MC, Cavill I, Weiss G, Iron, anaemia, and inflammatory bowel diseases. Gut 2004; 53: 1190-1197
5. Pizzii LT, Weston CM, Goldfarb NI, Moretti D, Cobb N, Howell JR, Infantinole A, Dimarino AJ, Cohen S. Impact of chronic conditions on quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis 2006; 12: 47-52
6. Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflamm Bowel Dis 2006; 12: 123-130
7. Cucino C, Sonnenberg A. Cause of death in patients with inflammatory bowel disease. Inflamm Bowel Dis 2001; 7: 250-255
8. Wilson A, Reyes E, Ofman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. Am J Med 2004; 116 Suppl 7A: 445-495
9. Bambach CP, Hill GL. Long term nutritional effects of extensive resection of the small intestine. Aust N Z J Surg 1982; 52: 500-506
10. Beeken WL. Absorptive defects in young people with regional enteritis. Pediatrics 1973; 52: 69-74
11. Beeken WL. Remediable defects in Crohn disease: a prospective study of 63 patients. Arch Intern Med 1975; 135: 686-690
12. Burbridge EJ, Huang SH, Bayless TM. Clinical manifestations of Crohn's disease in children and adolescents. Pediatrics 1975; 55: 866-871
13. Dyer NH, Child JA, Mollin DL, Dawson AM. Anaemia in Crohn's disease. Q J Med 1972; 41: 419-436
14. Ebinger M, Leidl R, Thomas S, Von Tirpitz C, Reinschagen M, Adler G, Konig HH. Cost of outpatient care in patients with inflammatory bowel disease in a German University Hospital. J Gastroenterol Hepatol 2004; 19: 192-199
15. Ershler WB, Chen K, Reyes EB, Dubois R. Economic burden of patients with anemia in selected diseases. Value Health 2005; 8: 629-638
16. Gasché C, Reinsch W, Lochs H, Parsaeei B, Bakos S, Wyatt J, Fueger GF, Gangl A. Anemia in Crohn's disease. Importance of inadequate erythropoietin production and iron deficiency. Dig Dis Sci 1994; 39: 1930-1934
17. Greenstein AJ, Kark AE, Dreiling DA. Crohn's disease of the colon. II. Controversial aspects of hemorrhage, anemia and rectal involvement in granulomatous disease involving the colon. Am J Gastroenterol 1975; 63: 40-48
18. Harries AD, Fitzsimons E, Dew MJ, Heatley RV, Rhodes J. Association between iron deficiency anaemia and mid-arm circumference in Crohn's disease. Hum Nutr Clin Nutr 1984; 38: 47-53
19. Hoffbrand AV, Stewart JS, Booth CC, Mollin DL. Folate deficiency in Crohn's disease: incidence, pathogenesis, and treatment. Br Med J 1968; 2: 71-75
20. Horina JH, Petritsch W, Schmid CR, Reicht G, Wenzl H, Silly H, Krejs GJ. Treatment of anemia in inflammatory bowel disease with recombinant human erythropoietin: results in three patients. Gastroenterology 1993; 104: 1828-1831
21. Lakatos L, Pandur T, David G, Balogh Z, Kuronya P, Tollas A, Lakatos PL. Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. World J Gastroenterol 2003; 9: 2300-2307
22. Niv Y, Abukasis G. Prevalence of ulcerative colitis in the Israeli kibbutz population. J Clin Gastroenterol 1991; 13: 98-101
23. Niv Y, Torten D, Tamir A, Epstein L. Incidence and prevalence of ulcerative colitis in the upper Galilee, Northern Israel, 1967-1986. Am J Gastroenterol 1990; 85: 1580-1583
24. Oldenburg B, Koningsberger JC, Van Berge Henegouwen GP, Van Asbeck BS, Marx JJ. Iron and inflammatory bowel disease. Aliment Pharmacol Ther 2001; 15: 429-438
25. Reilly J, Ryan JA, Strole W, Fischer JE. Hyperalimentation and deficiencies in inflammatory bowel disease. Am J Surg 1976; 131: 192-200
26. Revel-Vilk S, Tamary H, Broide E, Zoldan M, Dinari G, Zahavi I, Yaniv I, Shamir R. Serum transferrin receptor in children and adolescents with inflammatory bowel disease. Eur J Pediatr 2000; 159: 585-589
27. Schreiber S, Howaldt S, Schmoo M, Nikolaus S, Bauditz J, Gasché C, Lochs H, Raedler A. Recombinant erythropoietin for the treatment of anemia in inflammatory bowel disease. N Engl J Med 1996; 334: 619-623
28. Vijverman A, Piront P, Belaiche J, Louis E. Evolution of the prevalence and characteristics of anemia in inflammatory bowel diseases between 1993 and 2003. Acta Gastroenterol Belg 2006; 69: 1-4
29. Walker AM, Szneke P, Bianchi LA, Field LG, Sutherland LR, Dreyer NA. 5-Aminosalicylates, sulfasalazine, steroid use, and complications in patients with ulcerative colitis. Am J Gastroenterol 1997; 92: 816-820
30. Werlin SL, Grand RJ. Severe colitis in children and adolescents: diagnosis, Course, and treatment. Gastroenterology 1977; 73: 828-832
31. de Vizia B, Poggi V, Conenna R, Fiorillo A, Scippa L. Iron absorption and iron deficiency in infants and children with gastrointestinal diseases. J Pediatr Gastroenterol Nutr 1992; 14: 21-26
32. Ormerod TP. Observations on the incidence and cause of anaemia in ulcerative colitis. Gut 1967; 8: 107-114
33. Ormerod TP. Anaemia in ulcerative colitis. Proc R Soc Med 1968; 61: 931

www.wjgnet.com
efficacy and implications for research and programs. J Nutr 2002; 132: 813S-819S
73 Silverstein SB, Rodgers GM. Parenteral iron therapy options. Am J Hematol 2004; 76: 74-78
74 Bartels U, Pedersen NS, Jarnum S. Iron absorption and serum ferritin in chronic inflammatory bowel disease. Scand J Gastroenterol 1978; 13: 649-656
75 GASche C, Dejaco C, Reinisch W, Tillinger W, Walldhoer T, Fueger GF, Lochs H, Gangl A. Sequential treatment of anemia in ulcerative colitis with intravenous iron and erythropoetin. Digestion 1999; 60: 262-267
76 GASche C, Walldhoer T, Feichtenschlager T, Male C, Mayer A, Mittermaier C, Petritsch W. Prediction of response to iron sucrose in inflammatory bowel disease-associated anemia. Am J Gastroenterol 2001; 96: 2382-2387
77 Mamula P, Piccoli DA, Peck SN, Markowitz JE, Baldassano RN. Total dose intravenous infusion of iron dextran for iron-deficiency anemia in children with inflammatory bowel disease. J Pediatr Gastroenterol Nutr 2002; 34: 286-290
78 Schröder O, Schrott M, Blumenstein I, Jahnel J, Dignass AU, Stein J. A study for the evaluation of safety and tolerability of intravenous high-dose iron sucrose in patients with iron deficiency anemia due to gastrointestinal bleeding. Z Gastroenterol 2004; 42: 663-667
79 Auerbach M, Ballard H, Glaspy J. Clinical update: intravenous iron for anemia. Lancet 2007; 369: 1502-1504
80 Chertow GM, Mason PD, Vaage-Nilsen O, Ahlmén J. Update on adverse drug events associated with parenteral iron. Nephrol Dial Transplant 2006; 21: 378-382
81 Kulnigg S, Stoinov S, Simanenkov V, Duder LV, Karnafel W, Garcia LC, Sambuelli AM, D’Haens G, Gasche C. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. Am J Gastroenterol 2008; 103: 1182-1192
82 Demirtürk I, Hülagü S, Yaylaci M, Altin M, Ozel M. Serum erythropoietin levels in patients with severe anemia secondary to inflammatory bowel disease and the use of recombinant human erythropoietin in patients with anemia refractory to treatment. Dis Colon Rectum 1995; 38: 896-897
83 Koutroubakis IE, Karmiris K, Makreas S, Xidakis C, Ninikaki M, Kouroumalis EA. Effectiveness of darbepoetin-alfa in combination with intravenous iron sucrose in patients with inflammatory bowel disease and refractory anemia: a pilot study. Eur J Gastroenterol Hepatol 2006; 18: 421-425
84 Dohil R, Hassall E, Wadsworth LD, Israel DM. Recombinant human erythropoietin for treatment of anemia of chronic disease in children with Crohn’s disease. J Pediatr 1998; 132: 155-159
85 Sandborn W. Erythropoietin for inflammatory bowel disease anemia. Gastroenterology 1997; 112: 660-661
86 Christodoulou DK, Tsianos EV. Anemia in inflammatory bowel disease - the role of recombinant human erythropoietin. Eur J Intern Med 2000; 11: 222-227

S- Editor Tian L  L- Editor Cant MR  E- Editor Lin YP