



Intravenous Iron in Inflammatory Bowel Disease

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One of the key symptoms of inflammatory bowel diseases (IBD) is anemia. The reported prevalence of IBD-associated anemia varies between 6% and 74%. Although the therapy of the underlying disease has improved during the past decade, significant anemia continues to be a relevant burden. Iron deficiency and anemia of chronic disease are frequently combined in these patients. Oral iron therapy has been associated with flares in ulcerative colitis, similar to what has been observed in animal models of colitis. Parenteral iron supplementation has become the preferred route as the safety and efficacy of iron sucrose has been demonstrated in several trials. Open questions relate to the use of iron sucrose for prevention of anemia, the target hemoglobin levels, and the immunologic role of iron in the setting of chronic bowel inflammation.

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Inflammatory bowel diseases (IBD) are a group of intestinal diseases that share a variety of symptoms such as chronic or recurrent diarrhea, abdominal pain, fever, thrombocytosis, and anemia. Two major forms of IBD are typically recognized: Crohn's disease and ulcerative colitis. Further subforms involve indeterminate colitis and microscopic (collagenous) colitis. Besides intestinal inflammation, this syndrome is associated with extra-intestinal manifestations of the skin (pyoderma gangrenosum, erythema nodosum), joints (altrhalgia, peripheral arthritis, or spondylarthritis), or eyes (uveitis or conjunctivitis). Furthermore, IBD runs together with chronic inflammatory diseases of other tissues such as psoriasis, primary sclerosing cholangitis, and ankylosing spondylitis.

The cause of IBD has not been identified yet. Several genetic loci have been linked to IBD at various chromosomes (IBD1 to IBD8).¹ At some of these loci the responsible gene with its variants has been identified (eg, IBD1 locus: CARD15 or Nod2).² However, the genetic mutations explain only part of the general disease susceptibility.³ Environmental factors that have changed over the past 100 years are significantly more important. In this respect, Crohn's disease has been first described in the early 1900s.⁴ Epidemiologic data demonstrate a significant increase in both Crohn's disease and ulcerative colitis in Western Europe during the 1960s and

1970s, while these diseases were significantly less common in populations of Eastern or Central Europe, which had been separated from Western life style (by the Iron Curtain).⁵ Incidence numbers are still picking up to almost 15/100,000 in Canada for Crohn's disease.⁶ Prevalence ranges between 200 and 400/100,000. The best understood environmental factor is cigarette smoking.⁷ It has an aggravating effect on Crohn's disease and is associated with a higher number of flares, more steroid intake, and frequent operations. In contrast, smoking and nicotine therapy protect from ulcerative colitis.⁸ It is not uncommon that patients develop their first flare when they quit smoking. This just points to the fact that we are dealing with two distinct phenotypes that share symptoms and genetic predisposition but are triggered by different environmental factors and display different types of intestinal inflammation.

IBD-Associated Anemia

Hematologic changes such as anemia and thrombocytosis are among the most common symptoms of these diseases with a prevalence between 6% and 74% (Table 1). Anemia has long been regarded as a marker of inflammation. This is well established since hematocrit or hemoglobin are the only laboratory parameters that are included in disease activity scores such as Crohn's disease activity index or the colitis activity index.^{9,10} However, the underlying cause of anemia is considered to be primarily due to chronic intestinal blood loss through ulcerations, which leads to a negative iron balance and thereby to the development of iron-deficiency anemia. Mediators of intestinal inflammation such as tumor necrosis factor (TNF)- α or interferon (INF)- γ , however, may also af-

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Table 1 Prevalence of Anemia in Inflammatory Bowel Disease

Study	Year of Publication	Country	n	Phenotype	Prevalence (%)
Vijverman et al ³⁶	2006	Belgium	80 (1993) 90 (2003)	IBD	34 (1993) 17 (2003)
Ershler et al ³⁷	2005	USA	7,200	IBD	12.9
Ebinger et al ³⁸	2004	Germany	390	Crohn's disease	6.2
Lakatos et al ³⁹	2003	Hungary	254	Crohn's disease	57.8
Oldenburg et al ⁴⁰	2001	Netherlands	?	Crohn's disease	29.0
Revel-Vilke et al ⁴¹	2000	Israel	63	IBD	41.3
Schreiber et al ⁴²	1996	Germany	334	Crohn's disease	26.3
Gasche et al ¹⁵	1994	Austria	49	Crohn's disease	32.7
Horina et al ⁴³	1993	Austria	85	IBD	32.9
Harries et al ⁴⁴	1984	England	55	Crohn's disease	43.6
Bambach and Hill ⁴⁵	1982	Australia	36	Crohn's disease	16.7
Werlin and Grand ⁴⁶	1977	USA	19	Severe Colitis	73.7
Reilly et al ⁴⁷	1976	USA	9	Small bowel Crohn's disease	33.3
Reilly et al ⁴⁸	1976	USA	14	Large bowel Crohn's disease	71.4
Greenstein et al ⁴⁹	1975	USA	160	Crohn's disease	71.3
Burbige et al ⁵⁰	1975	USA	58	Crohn's disease	51.7
Beeken ⁵¹	1975	USA	63	Crohn's disease	69.8
Beeken ⁵²	1973	USA	11	Crohn's disease	72.7
Dyer et al ⁵³	1972	England	63	Crohn's disease	63.5
Hoffbrand et al ⁵⁴	1968	England	64	Crohn's disease	43.8

fect erythropoiesis and iron metabolism, which reflects the presence of anemia of chronic disease (ACD). Iron deficiency and ACD are frequently combined in this type of patient.¹¹ Besides, various pharmacologic drugs that are used for treatment of IBD, eg, sulfasalazine, mesalazine, azathioprine, and 6-mercaptopyrin, may interfere with erythropoiesis. Extensive ileal resection in Crohn's disease may be associated with vitamin B₁₂ deficiency. A series of case reports on hemolytic anemias mainly associated with ulcerative colitis has highlighted a possible shared autoimmune mechanism.¹² Also, myelodysplastic syndrome, aplasia, and inborn disorders of erythropoiesis have been reported.

The diagnosis of iron deficiency in the setting of ACD may be difficult. Bone marrow studies in patients with rheumatoid arthritis have shown that even ferritin levels above 55 $\mu\text{g/L}$ do not necessarily mean that iron is present.¹³ Therefore, in the recent literature a ferritin cutoff level of 100 $\mu\text{g/L}$ is recommended when ACD is also present.¹⁴ However, in a series of 49 Crohn's patients, the average ferritin level was 28.7 $\mu\text{g/L}$ in anemic cases and 63.2 $\mu\text{g/L}$ in non-anemic cases, pointing to the importance of iron deficiency.¹⁵ As indicated above, ACD alters the body's iron metabolism possibly through the expression of hepcidin.¹⁶ Hepcidin blocks iron release from the macrophages and therefore reduces the availability of iron in the bone marrow. In our set of Crohn's patients, the average transferrin saturation was 6.2% in anemic cases and 11.5% in non-anemic cases, which is quite low and fits with the iron-withholding model in ACD. Last but not least, erythropoietin levels may be inappropriately low when compared to the corresponding hemoglobin level. Indeed, several patients with hemoglobin levels as low as 8 g/dL did not display a corresponding elevation of the erythropoietin concentration.¹⁵

Oral or Parenteral Iron Therapy

Under physiologic conditions, about 1 mg of iron is absorbed every day. Studies have shown that, in the setting of iron deficiency, iron absorption may increase. To prevent iron overload, however, iron absorption is tightly regulated. In ACD increased hepcidin may inhibit iron absorption.¹⁷ When considering oral iron therapy, more than 90% of a given dose is not absorbed and passes with stool. However, when this non-absorbed iron is in contact with mucosal ulcerations in IBD it may induce oxidative stress (through the Fenton reaction) and trigger local inflammation.¹⁸ In fact, reported side effects in Crohn's patients differ from controls.¹⁹ It was observed that IBD patients mostly complain about an increase in stool frequency while control individuals typically report constipation upon oral iron therapy. Studies from Norway also showed a reduction of oxygen scavengers upon oral iron therapy, which is indicative of oxidative stress at the mucosal surface.¹⁹ A recent study from England demonstrated a worsening of clinical and mucosal disease activity in patients with ulcerative colitis treated with ferrous sulfate for four weeks.²⁰ This is in line with several animal models of colitis that showed an increase in oxidative stress, proinflammatory cytokine production or mucosal inflammation when treated with iron-enriched drinking water.²¹⁻²⁵ Because of these limitations, parenteral iron therapy should be considered in IBD.²⁶

Most of the available data on parenteral iron replacement therapy concern iron sucrose. Iron sucrose is a semi-stable iron-sugar complex with a molecular weight between 34 and 60 kd. When applied intravenously, the complexed iron is taken up by macrophages and iron is released secondarily to transferrin. However, parts of the sugar-bound ferric iron are

directly released to transferrin or other negatively charged serum proteins, such as albumin. Single doses up to 7 mg/kg body weight can be given in IBD and are well tolerated.²⁷ In controlled trials, short infusions of 200 to 300 mg iron sucrose diluted in sodium chloride were typically applied once or twice per week. In a controlled randomized trial for treatment of anemia in Crohn's disease 2,000 mg of iron sucrose was infused over an 8-week period.²⁸ The iron sucrose group showed a significant increase in hemoglobin levels from 8.5 g/dL to almost 12 g/dL. When iron sucrose was combined with erythropoietin, the increase was even faster and higher, with hemoglobin levels reaching about 13.5 g/dL at 8 weeks. During a second, open phase, an additional 1,600 mg of iron sucrose was applied. On this regimen and in combination with erythropoietin, anemia was successfully managed in all patients and led to an improvement in quality of life.

Another prospective trial tested the same regimen for ulcerative colitis-associated anemia. Response rates to iron sucrose were comparable to Crohn's disease (65% in 4 weeks, 85% in 8 weeks) and again the drug was well tolerated.²⁹ Side effects were limited to pain at the infusion site, bitter taste, temporary hypotension, fever, or an increase in diarrhea. No anaphylactic reactions or severe side effects were observed. In a retrospective analysis of 61 anemic IBD patients with a mean hemoglobin of 9.7 g/dL, Bodemar and colleagues reported a 60% response rate within 8 weeks and 91% within 12 weeks.³⁰ The total iron sucrose dose was 1.4 g on average and 32% of patients needed a second treatment series. This study best reflects the use of iron sucrose in clinical practice.

In a German multicenter trial, iron sucrose was compared to oral iron over a 6-week period.³¹ In this trial the head to head comparison between oral and intravenous iron led to a comparable increase in hemoglobin levels; however, only the intravenous group showed a gain in serum ferritin concentrations indicative of building up iron stores (the ferritin was approximately 200 μ g/L at week 6). In contrast, the oral iron group did not build up any iron reserve. In another comparative, crossover trial, the clinical disease activity increased in the oral iron group while it was unchanged in the intravenous iron group, again questioning the safety of oral iron therapy in IBD.³²

To answer the question whether patients will respond to iron sucrose or would need additional erythropoietin therapy, a large Austrian multicenter study was performed.³³ Of eight variables that had been tested as predictive parameters, serum erythropoietin, transferrin, and the soluble transferrin receptor concentrations proved to be of good predictive value. The quality of these parameters was similar; the clinical availability of transferrin, however, is best. Individuals with high pretreatment transferrin values are likely to respond to iron sucrose. As soon as the transferrin level is below 3 g/L this likelihood drops below 50%. In such individuals, it is recommended to start with a combination therapy of iron sucrose and erythropoietin.²⁶ In this regard, it is interesting to note that the endogenous erythropoietin level drops rapidly upon iron sucrose therapy (Fig 1). The mechanism behind this observation is unknown; however, we believe that it is rapid

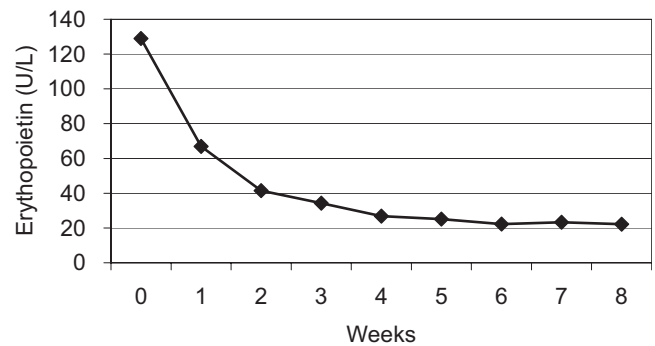


Figure 1 Serum erythropoietin levels were measured in 20 Crohn's patients that had been treated with iron sucrose (2000 mg) as part of a randomized controlled trial.²⁸ The mean erythropoietin levels dropped within 2 weeks of therapy before an increase in hemoglobin was seen. The mechanism behind this observation is unknown. However, the kinetic is suggestive of fast erythropoietin utilization that is caused by stimulation of erythropoiesis (through iron sucrose) rather than suppression of erythropoietin production.

erythropoietin utilization by the bone marrow rather than lack of erythropoietin production.

The Future

Data are accumulating indicating that in the setting of IBD-associated anemia appropriate interventions increase the quality of life²⁸ and possibly also the cognitive functions.³⁴ In some studies, the disease-specific quality-of-life scores, such as the Inflammatory Bowel Disease Questionnaire (IBDQ) scores, also improve without any change in concomitant IBD-specific therapy.²⁰ A number of questions remain: What is the appropriate timing to start intravenous iron therapy? Do we need to wait for the hemoglobin level to drop below a certain trigger, or should we already prevent anemia by ensuring high iron stores? What is the appropriate hemoglobin target level? In the oncology setting, improvements in quality of life paralleled hemoglobin increases up to 14 g/dL.³⁵ Also, what is the appropriate ferritin target level that reflects adequate amounts of iron stores? Lastly, how does iron therapy affect the underlying inflammatory disease? Data from animal models and colitis patients are provoking the notion that oral iron therapy should be avoided in the IBD setting. Further studies are needed that investigate the immunological consequences of iron in the pathophysiology of chronic intestinal inflammation.

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