

## Clinical Viewpoints

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# Anemia in IBD: The Overlooked Villain

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**Summary:** During the past decade relevant progress has been made in the understanding and treatment of IBD-associated anemia. Effective replacement of iron deficits has become safe by using novel intravenous iron preparations such as iron sucrose. The ability of erythropoietin to interfere with key mechanisms of myelosuppression in anemia of chronic diseases also benefits patients with IBD-associated anemia. Concerns about cost effectiveness have been raised and weighed against the

potential improvement in quality of life. Gastroenterologists who are caring for IBD patients should be concerned with low hemoglobin levels, since the quality of life in these patients can be as low as in anemic patients with advanced cancer. Also provided is a structured approach to cost-effective therapy. **Key Words:** Anemia—Iron sucrose—Erythropoietin—Inflammatory bowel diseases.

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### PAYING ATTENTION

Compared with the average awareness of other extraintestinal disease complications such as arthritis or osteopathy, the topic of anemia in inflammatory bowel disease (IBD) receives little attention, if any. A possible explanation for this might be low incidence of IBD-associated anemia, which, however, is not true. Most studies demonstrate that at a random point in time one-third of the IBD population suffers from anemia (1). In fact intestinal bleeding (either visible blood in ulcerative colitis [UC] or occult blood in Crohn's disease [CD]) is a major symptom of IBD itself, and a drop in red blood cell count occurs with each flare-up. It is true that anemia

may occur asymptotically; however, the term “asymptomatic” reflects that impairment in quality of life, cognitive functions, or ability to work may go unrecognized by patients and doctors. This is a non-IBD-specific, general characteristic of anemia and is noticed not only by hematologists, but also nephrologists, gastroenterologists, and hepatologists who care for the majority of anemic patients. Gastroenterologists could learn from the experience of nephrologists who have learned their lesson in the recent past (2,3). They showed that the process of adaptation to chronic anemia was in fact adaptation to a lower quality of life and consequently changed their treatment plans.

In this article I will extend on a recent overview published in *Inflammatory Bowel Diseases* (4), and draw the reader's attention to the progress since then. My goal is to provide simple tools for a step-wise approach to understanding IBD-associated anemia and to give a practical strategy for planning effective therapy. I will focus on

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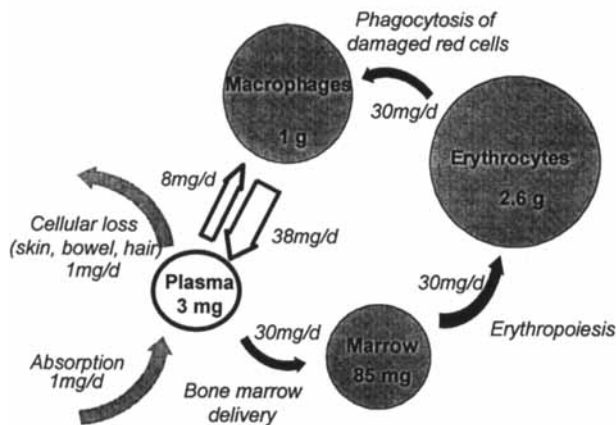
iron deficiency and the mechanisms of chronic disease, and not on anecdotal contributors to IBD-associated anemia such as glucose-6-phosphate dehydrogenase deficiency, autoimmune hemolysis, myelosuppression, vitamin B12, or folate deficiencies (4).

## BASIC ASPECTS OF IRON METABOLISM

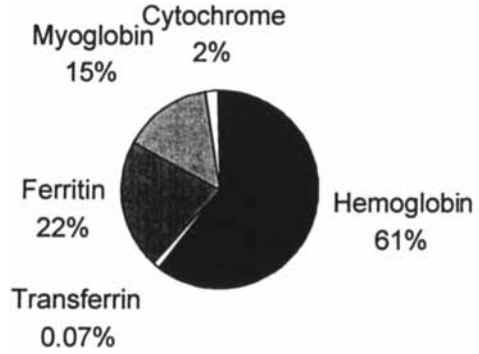
### Iron Uptake

Iron passes from the gut lumen through the apical and basolateral membrane of enterocytes of the duodenum and the upper jejunum. Usually every day, 1–2 mg are absorbed, and the same quantity is lost through epithelial turnover in the skin and gut (Fig. 1). Iron balance in the body is maintained by regulation of iron absorption. Internalized iron binds to transferrin (Tf) and is transported in the plasma. This plasma iron pool represents a very small percentage of total iron, which in adults is between 3.5 and 5.0 g, mainly bound to hemoglobin (Hb) (Fig. 2). This is important when measuring plasma iron concentration or Tf saturation.

The bilobal nature of Tf contains two iron binding sites. Under physiological conditions about 30–40% of these binding sites are occupied (resembling Tf saturation). Tf-bound iron is taken up by the Tf receptor (TfR) into target cells, primarily erythroid progenitor cells but also immune or liver cells. Iron is an important cofactor



**FIG. 1.** Iron metabolism in adult males. Every day, 1–2 mg of elemental iron are absorbed in the proximal small bowel and bound to transferrin. Transferrin-bound plasma iron is mainly transported to the bone marrow and used for erythropoiesis (30 mg/day). A balanced amount of iron is released daily after erythrocyte damage. Macrophages phagocytize damaged red blood cells, process Hb iron, and return it to plasma transferrin. There is also continuous backflow from transferrin-bound plasma iron into iron stores (RES, reticulo endothelial system). Under physiological conditions, iron leaves the body through shedded skin cells, intestinal epithelial cells, or through hair. In females most iron is lost with menstrual blood.



**FIG. 2.** Distribution of total body iron (3.5–5.0 g) in adults. More than one-half of total iron in the body is bound to hemoglobin, and more than one-third to intracellular ferritin and myoglobin. However, the function of every cell in the body depends on a small amount of iron in specific enzymes such as mitochondrial cytochromes. When relating the little proportion of transferrin-bound iron to its importance in body iron distribution, the apparent limits of systemic iron delivery become obvious.

of many intracellular proteins or enzymes such as mitochondrial cytochromes or ribonucleotide reductase, and is needed in every cell of the body.

After binding of Tf to the receptor, the complex enters the cell by formation of an endosome (5). The pH within the endosome is lowered by an energy-dependent proton pump, iron is released from Tf, and may diffuse into the cytosol. The apotransferrin-TfR complex is then returned to the plasma membrane where apotransferrin (which has a lower affinity for the receptor than Tf) is released and the TfR is free to repeat the process.

A truncated form of the Tf receptor molecule (lacking cytoplasmic and transmembrane domains) can be detected in human serum. This soluble TfR (sTfR) is the result of shedding TfR from the cell surface by proteolytic cleavage (6), and is proportional to the total amount of surface TfR (7). Elevated levels of sTfR indicate iron deficiency and high-rate erythropoiesis (8,9). Despite the fact that cytokines and nitric oxide may interfere with TfR expression (10), the sTfR is reported to distinguish between iron deficiency alone and the combination of iron deficiency and anemia of chronic disease (11).

### Regulation of Intracellular Iron Concentration

Intracellular iron deficiency upregulates cellular TfR expression to counteract iron intracellular iron needs (12). TfR expression is regulated posttranscriptionally by interaction between iron-regulatory proteins (IRP) and the iron-responsive elements (IRE) present on the 3'-untranslated region of its mRNA (13). The intracellular iron concentration changes the affinity of IRP to bind to IRE: Low iron concentrations cause high affinity binding

and vice versa. Binding of IRP to IRE at the 3'-untranslated region of TfR mRNA protects it from degradation and increases TfR expression (in order to enhance iron uptake). Binding of IRP to IREs located at the 5'-untranslated regions of ferritin or 5-aminolevulinic acid (ALA-S, the key enzyme of hb biosynthesis) synthetase mRNAs represses translation and protein synthesis (14). In contrast, high intracellular iron concentrations cause TfR degradation and induce ferritin and ALA-S expression.

Ferritin consists of an apoprotein shell, made from a composition of 24 heavy and light chain subunits, enclosing a core of iron that may contain up to 4,500 atoms. The main function of ferritin is to provide an intracellular pool of iron that may be used for synthesis of iron-dependent proteins. The amount of ferritin in circulation is directly related to its intracellular quantity and generally reflects the amount of iron resources. Inflammation and neoplasia are associated with a significant rise in serum ferritin levels. The response of serum ferritin to inflammation suggests that it acts like an acute phase protein. As a result, inflammation can cause false elevations of ferritin levels or bring ferritin levels of patients with true iron deficiency into the normal range (18–300  $\mu\text{g/L}$ ). This phenomenon has been well studied in rheumatoid arthritis (15) and IBD (16), with subsequent adjustment of the lower ferritin limit to 55  $\mu\text{g/L}$ .

### Role of Iron for Hemoglobin Syntheses

Most importantly, Hb synthesis depends on availability of intracellular iron in erythroid precursor cells. ALA-S is regulated parallel to ferritin by interaction of IRP with IRE on the 5'-untranslated region of its mRNA. Thus, Hb biosynthesis only starts when intracellular iron concentrations are high. Hb itself holds about 60% of total body iron (Fig. 2). As iron itself regulates the synthesis of related proteins, iron metabolism can be observed by measurement of these proteins (mainly Hb, Tf, sTfR, and ferritin). As pointed out above, the plasma iron concentration itself is only a poor diagnostic tool.

### Immunologic Properties of Iron

Iron is not only essential for erythropoiesis, growing microorganisms, or tumor cells but is also crucial for proliferation and function of immune cells. Iron plays a critical role in macrophage-mediated cytotoxicity by catalyzing the production of reactive oxygen species. In reverse, oxidative stress and nitric oxide stimulate the binding of IRP to IRE loops and interfere with expression of TfR and ferritin (14,18). Iron-loaded macro-

phages also exhibit reduced interferon- $\gamma$  responsiveness, TNF- $\alpha$  production, and NO formation (17).

## IRON METABOLISM IN IBD

IBD-associated anemia is a unique example of the combination of chronic iron deficiency and anemia of chronic diseases (ACD). Iron deficiency in IBD results mostly from chronic intestinal blood loss (19). Occasionally iron absorption may be impaired in the duodenum or upper jejunum of CD patients (20). In general, however, the iron absorption capacity in CD or UC is normal. Regarding chronic intestinal bleeding of IBD patients, the increase in iron loss may exceed the ability of iron absorption, which can result in a negative iron balance. Dietary restrictions may also contribute to a general reduction of total body iron.

Beside deficiencies in total body iron, chronic inflammation mediates mechanisms of iron withholding from the plasma pool. Upregulation of ferritin and downregulation of Tf synthesis are part of the acute phase response. This leads to a shortage in Tf-bound plasma iron, also referred as functional iron deficiency (21). This term describes the inability of the iron transportation system to deliver adequate amounts of iron from the storage pool to the bone marrow.

## ANEMIA OF CHRONIC DISEASES

The production of inflammatory cytokines within inflamed bowel segments not only perpetuates the inflammatory reaction within the bowel, but also has important systemic effects on bone marrow stem cells. The term ACD was first used by Cartwright (22). The understanding of the interaction between inflammatory cytokines and erythropoiesis has grown in past decades (23,24). Interferon- $\gamma$ , IL-1, and TNF- $\alpha$ , as well as IL-6, are players in this field. The mechanisms of ACD are similar in different diseases such as rheumatoid arthritis, IBD, chronic infection, or malignancy. Both ineffective erythropoiesis and reduced red blood cell life span contribute to ACD.

Three important mechanisms have been identified:

1. Iron withholding from the plasma with inadequate delivery to the bone marrow, so called functional iron deficiency (mostly mediated by IL-1, TNF- $\alpha$ )
2. Direct inhibition of erythropoiesis at the level of BFU-E- and CFU-E (by interferon- $\gamma$ ) (25)
3. Inhibition of erythropoietin (EPO) production (by IL-1, TNF- $\alpha$ , IL-6) (26)

In vitro studies indicated that interferon- $\gamma$ -induced inhibition of erythropoiesis may be overruled by addition of EPO (27).

With an impaired autologous EPO production, this potential EPO effect (to overrule interferon- $\gamma$ -induced inhibition of erythropoiesis) provides the experimental basis for treatment of ACD with rHuEPO.

From potential mediators of ACD, IL-6, as systemically upregulated in flare-ups of IBD (28), has also been investigated for its potential impact on IBD-associated anemia. The dominance of iron deficiency, however, might have obscured any relation of this cytokine to the occurrence of anemia (1). The same study showed that serum EPO levels are inadequately low to the degree of anemia. The latter finding was supported by the observation that some IBD patients who had anemia despite replete iron stores responded well to this erythroid growth factor (29).

## ERYTHROPOIETIN

The hematopoietic system must maintain a steady-state level of circulating blood cells and respond to acute challenges. Through constant turnover, hematopoietic cells are removed from the system after damage. This is particularly true for red blood cells, which are eliminated after an average lifespan of 120 days. Various hematopoietic growth factors have been identified that ensure a proper balance of both the broad spectrum of blood cells and their specific counts. EPO has been identified as one of the key regulators of red blood cell development. Isolation and molecular cloning enable large amounts of this molecule to be synthesized and used for treatment of various forms of anemia (30–34). EPO interacts with its receptor, which is mainly expressed on erythroid progenitor cells such as BFU-E and CFU-E and causes four effects (35): maintaining viability, promoting cell division, increasing Hb synthesis, and fostering morphological maturation. The specificity of the EPO effect limits the array of possible adverse events. In IBD patients, only local pain at the injection site was reported. Thrombosis, hypertension, and seizures may, however, occur in renal patients. The expression of EPO receptors on some endothelial cells and in the brain may partially contribute to these findings.

## TREATMENT OF IBD-ASSOCIATED ANEMIA

### Definition of Goals

Besides the change in Hb levels, the primary therapeutic goal is to improve quality of life. It was quite

amazing when we first realized that the quality of life in our anemic CD patients was as low as in anemic patients with advanced cancer (36). Effective therapy, however, improved not only the patients' hematocrit but also their general well-being causing an average drop in the Crohn's Disease Activity Index of 120 points (37). Specifically, well-being, mood, physical ability, and attending social activities accounted for most of the improvement in quality of life. Other recorded improvements are the relief of disturbed sleep or erectile dysfunction and increase in sexual desire. We should keep in mind that the normalization of Hb levels might have the same impact on quality of life as the normalization of bowel movements or abdominal pain.

Blood Hb should be considered as a convenient monitor of a treatment effect. For study purposes, patients with Hb  $\leq 10.5$  g/dl are regarded to have severe anemia. A response to a specific intervention is usually defined by an increase in Hb of  $\geq 2.0$  g/dl. Studies in iron-deficient (ferritin, 12  $\mu$ mg/L) and nonanemic (Hb  $> 12.0$  g/dL) high school students showed that cognitive performance can be further improved by oral iron supplementation (38). This finding questions an Hb of 12.0 g/dl as the final therapeutic goal. It has been suggested to set the Hb target value above 13.0 g/dl. In dialysis patients, a rise in Hb was shown to improve intellectual function (39,40). We assume the same effect in IBD patients.

As pointed out above, the mechanisms of IBD-associated anemia involve iron deficiency and ACD. Treatment strategies should be directed against both.

## Iron Therapy

### Oral Iron Preparations

Oral iron supplements contain iron in the form of ferrous salts or iron polysaccharide (ferrous sulfate, ferrous gluconate, ferrous fumarate, or iron polymaltose complex). Although there are different galenic formulations available, no clear evidence supports the superiority of any specific agent. In general, enteric-coated formulations should be avoided, because they may release their iron content beyond the intestinal side of maximal iron absorption. The efficacy of oral iron preparations in patients with IBD may be hindered by two important factors:

1. *Patient compliance:* Patients' compliance of taking oral iron preparations decreases with gastrointestinal side effects. Nausea, bloating, diarrhea, and upper gastrointestinal pain are frequent side effects in the IBD population. The cause of these symptoms is not

well understood but may involve intestinal formation of free oxygen radicals (41).

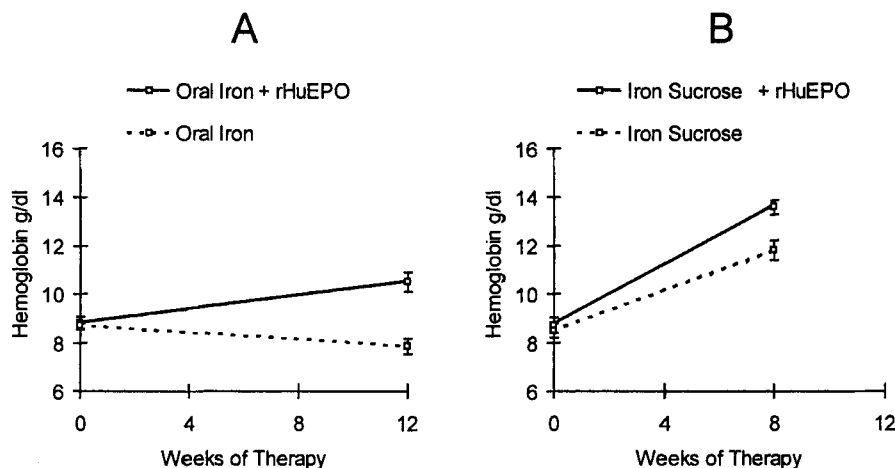
2. *High iron needs.* The iron requirement to correct anemia in IBD can be estimated by the approximation that an increase of 1 g/dl serum Hb corresponds to 150 mg iron. Anemic disease states in IBD are also associated with exhausted iron reserve pools. The total amount of iron needed can be estimated as follows (42): Iron needed for Hb synthesis (mg) =  $(14.0 - \text{baseline Hb [in g/dl]}) \times 3.47 [\text{mg iron/g of Hb}] \times 0.6 [\text{dl of blood/kg body weight}] \times \text{body weight [in kg]}$ . Iron needed to fill reserve (mg) =  $400 \times [(\ln 250 - \ln 12) - (\ln \text{baseline ferritin} - \ln 12)]$ . Total iron requirement (mg) = iron Hb deficit (mg) + iron reserve deficit (mg); 14.0 is considered the intended posttreatment Hb concentration; 400 is an empirical constant and 250 is the target posttreatment ferritin level. If baseline ferritin is less than 12, the storage iron is taken as 0.

The projected total iron requirement for a 70 kg patient with Hb 8.0 g/dl and a ferritin of 15  $\mu\text{g/l}$  would be approximately 1,995 mg. Presuming a high iron absorption (10% of 200 mg/day), perfect compliance, and no continuous blood loss, oral iron therapy would need 100 days to replace such an iron deficit. Most patients, however, are continuously losing blood, have less daily absorption, and do not tolerate this amount of oral iron. A controlled trial in this setting has shown that oral iron substitution alone may not be sufficient to compensate ongoing blood loss (43) (Fig. 3A). Because of these limitations, the place for oral iron preparations is prevention (Hb > 12.0 g/dl) and moderate anemia only (Hb > 10.5 g/dl) (Fig. 5).

### Intravenous Iron Preparations

To overcome the obstacles of oral iron therapy, parenteral iron preparations are needed. The direct administration of iron into circulation requires formulation that prevents the cellular toxicity of iron salts (44). Three different products are available:

1. Iron dextran is a stable type of parenteral iron product. Its molecular weight is between 100 and 500 kD. These iron complexes show high structural homogeneity and thus only slow delivery of complexed iron to endogenous iron binding proteins. They are taken up from the plasma by the reticulo endothelial system (RES) (complexes are actively phagocytized by macrophages). Its plasma half-life is rather long (3 to 4 days). After intracellular degradation of the complex, iron may be released from macrophages, reenters the plasma, and becomes available for Hb synthesis. The release process, however, may be blocked by cytokines in systemic inflammation (see above). The dextran molecule may also cause well-known dextran-induced anaphylactic reactions. The stability of the dextran complex allows administration of high single doses.
2. Since the molecular weight of iron sucrose (which is the same as iron saccharate) is much smaller (30–100 kD), allergic reactions are less likely and there is no risk of dextran-induced anaphylactic reactions. Iron sucrose is a partially stable type of intravenous iron with medium kinetic degradation and partial uptake of released iron by apotransferrin or apoferritin but also by cells of the RES. Its half-life is relatively short (about 90 minutes).
3. Iron gluconate is a labile type with fast kinetic deg-



**FIG. 3.** Importance of parenteral iron support in IBD-associated anemia. Different outcomes of two controlled trials testing the efficacy of rHuEPO in IBD-associated anemia are plotted [Plot A: (43); Plot B: (37)]. Both studies were comparable in the baseline hemoglobin levels and total rHuEPO dosage (A: 200 U/kg, 2x/week for 12 weeks. B: 150 U/kg, 3x/week for 8 weeks). On oral iron therapy alone, the mean hemoglobin level dropped over the 12 week study period (A). In contrast, intravenous iron sucrose alone (B) caused a significant hemoglobin increase within 8 weeks that was even faster and higher with additional rHuEPO. Note that iron sucrose is more effective and less expensive (about US\$250) than a combination of oral iron and rHuEPO (about US\$3,000).

radation and only direct uptake to plasma proteins (apotransferrin, apoferritin, others). Potential toxicity of iron gluconate is referred to as oversaturation of Tf binding capacity (45). Free iron induces cell damage with clinical symptoms of capillary leak syndrome (dyspnea, edema, hypotension, and tachycardia). Because of more side effects and less efficacy, the intramuscular or subcutaneous route of parenteral iron administration is obsolete.

When we designed our first clinical trial in IBD-associated anemia, there was great concern over the risk of anaphylactic reactions to iron dextran. Therefore, we decided to use iron sucrose, which is tolerated well especially when used as a dilute solution (46–49). In past years, over 1,000 iron sucrose infusions were administered at the Vienna IBD center as part of controlled trials without serious adverse events (37,50). One infusion was prepared with 10 ml iron sucrose, corresponding to 200 mg Fe (III) (previous name: Ferrum Hausmann, new name: Venofer, Vifor International Inc., St. Gallen, Switzerland), diluted in 250 ml of a 0.9% sodium chloride solution and given intravenously over 60 minutes. At an infusion speed below 4 mg Fe/min, oversaturation of plasma iron binding capacity (released iron is mainly captured by Tf but also by albumin and other proteins) and the potential risk of a capillary leak syndrome (due to free iron) can be avoided. In our trials iron sucrose infusions were given twice during the first 2 weeks and once a week thereafter. After 4 weeks, approximately 65%, and after 8 weeks, 75% of patients responded to this regimen (receiving a total of 2,000 mg iron sucrose) (Fig. 3B).

### Recombinant Human Erythropoietin (rHuEPO)

Specific drugs for treatment of ACD have not yet been developed. Antiinflammatory drugs may have the potency to inhibit cytokine production but may also inhibit erythropoiesis themselves (e.g., azathioprine). rHuEPO has been studied in a variety of types of ACD (34). With concomitant oral iron therapy, the therapeutic potency of rHuEPO in IBD-associated anemia is limited by the rate of intestinal iron absorption (mean Hb increase 1.7 g/dl within 12 weeks) (Fig. 3A) (43). Only when iron sucrose is used as an iron supplement is rHuEPO able to exert its full potency on stimulating erythropoiesis (mean Hb increase 4.9 g/dl within 8 weeks) (Fig. 3B) (37). The 65–75% of IBD patients responding to iron sucrose alone points to the high cost-efficiency of this drug.

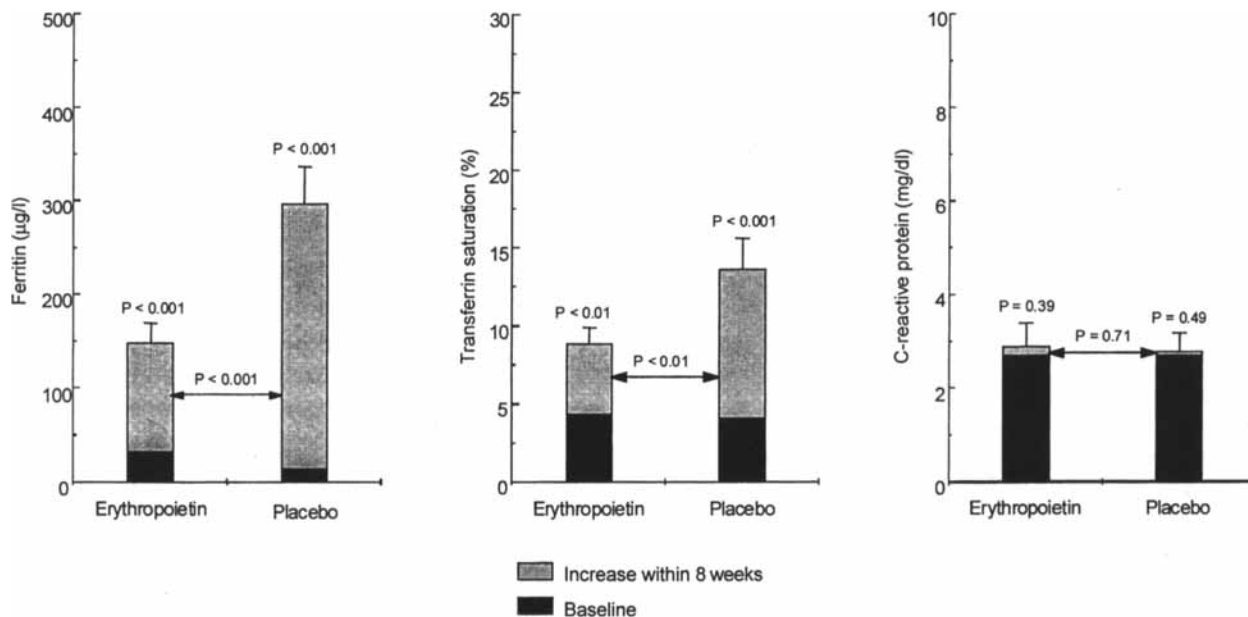
By inclusion of rHuEPO into the therapeutic plan, the use of parenteral iron in IBD-associated anemia is di-

rected into Hb synthesis rather than iron stores. When we tested the efficacy of rHuEPO versus placebo (while all patients received concomitant iron sucrose), Hb, serum ferritin levels, and Tf saturation increased in both treatment groups (rHuEPO and placebo). Previously unpublished data show that rHuEPO treated patients had less of an increase in ferritin or Tf saturation than the placebo group (Fig. 4), who had less rise in Hb levels (Fig. 3B). No change in C-reactive protein was observed indicating that the increase in ferritin is a true increase in iron storage rather than a change in inflammatory activity. This shows that rHuEPO directs plasma iron traffic towards erythropoiesis, which actually is the prime goal of this costly therapy in IBD-associated anemia.

When it became clear that iron sucrose is the most cost-effective therapy for CD-associated anemia, we tested the same treatment protocol in UC-associated anemia (50). Although it was harder to identify eligible patients (severe chronic anemia not responding to oral iron therapy is less common in UC than in CD), the results were similar: 65% of patients improved with iron sucrose within 4 weeks and 80% after 8 weeks. Those who did not respond within 8 weeks improved by addition of rHuEPO. At this point we realized that virtually all patients with IBD-associated anemia could be successfully treated with the combination of iron sucrose and rHuEPO. Further attempts were made to prevent blood transfusions in IBD, even in the setting of IBD-related surgery. By preoperative therapy with iron sucrose and rHuEPO, IBD patients were able to donate adequate amounts of autologous blood, thus preventing the need for intra- or postoperative homologous blood transfusions. The concept of rHuEPO for treatment of selected patients with IBD-associated anemia also proved to be safe and effective in children (51).

### Prediction of Response to Intravenous Iron Therapy

In terms of cost, rHuEPO should be reserved for patients not responding to intravenous iron. This relates to approximately one-third of patients with severe anemia ( $Hb \leq 10.5$  g/dL). The ability to predict this resistance to intravenous iron saves time and effort. A multicenter trial that aimed to identify parameters with predictive impact on the response to iron sucrose in IBD-associated anemia and involved 103 patients was recently completed (Gasche, et al., unpublished observations). Out of a series of baseline parameters chosen from indicators of iron deficiency and inflammatory activity, serum EPO levels, sTfR and Tf were most accurate for prediction of treatment response. An estimated 80% probability of treatment response was shown for serum EPO levels



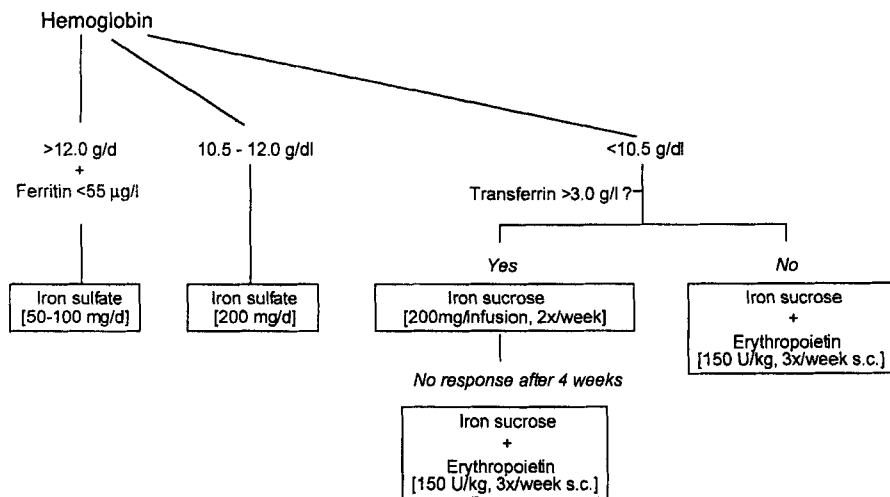
**FIG. 4.** Erythropoietin directs plasma iron traffic towards erythropoiesis rather than iron stores. Ferritin, transferrin saturation, and C-reactive protein levels at baseline and after therapy with iron sucrose (total dosage 2,000 mg in 8 weeks) (37). Data show that rHuEPO-treated patients who had a greater rise in Hb levels ( $\Delta$ Hb:  $4.9 \pm 1.1$  versus  $3.3 \pm 1.7$  g/dl,  $p = 0.004$ ) (Fig. 3B) had less of an increase in ferritin and transferrin saturation than the placebo-treated patients. Stable C-reactive protein levels indicated that the inflammatory activity was unchanged, and could not explain the pronounced increase in ferritin or transferrin saturation in the placebo patients.

above 166 U/L, sTfR above 75 nmol/L, or Tf above 3.83 g/L.

**STRATEGIC PLAN**

In regard to limited medical resources and the high cost of rHuEPO, it is our understanding that therapy with rHuEPO should be restricted to those patients who do not respond to iron sucrose alone. The ability to predict this group of patients by measurement of baseline EPO, Tf,

or sTfR levels is the basis for early classification of patients with severe anemia (Fig. 5). Those with low levels of these specific parameters will benefit most from concomitant rHuEPO therapy. From these parameters, Tf is likely to become the most practical. A baseline Tf concentration of 3.5 g/L relates to a 75% probability, 3.0 g/L to a 63% probability, and 2.5 g/L to a 50% probability of response to iron sucrose alone. We now start combined rHuEPO therapy in patients with a Tf of less than 3.0 g/L. After the therapeutic goal has been reached,



**FIG. 5.** Therapeutic algorithm in IBD-associated anemia. The primary parameter of anemia and iron deficiency is hemoglobin (Hb). In cases of Hb > 12.0 g/dl and low ferritin, a moderate dose (50–100 mg/d) of oral ferrous salts could improve cognitive function without causing side effects. This dose should also be sufficient for prevention of anemia. In patients with moderate anemia (Hb 10.5–12.0 g/d), high-dose oral iron preparations are necessary. At an Hb < 10.5 g/d, iron sucrose is the treatment of choice. Erythropoietin is indicated in patients with high likelihood of treatment failure (baseline transferrin < 3.0 g/l) or when Hb does not increase at least 2.0 g/dl within 4 weeks of therapy.

all patients can be switched to oral iron preparations (as long as they tolerate them). Oral iron might also work for patients with moderate anemia (Hb > 10.5 g/dl).

When working with IBD patients, there are good reasons to pay more attention to hemoglobin levels than ever before. Anemia in IBD is still a frequent complication, affecting cognitive function, ability to work, and general well-being, and can be effectively prevented or treated. We all know that none of our treatment options changes the chronicity of IBD. As long as we cannot cure these diseases, the optimization of supportive care is the way to improve our patients' quality of life.

## REFERENCES

- Gasche C, Reinisch W, Lochs H, et al. Anemia in Crohn's disease. Importance of inadequate erythropoietin production and iron deficiency. *Dig Dis Sci* 1994;39:1930-4.
- Macdougall IC. Strategies for iron supplementation: oral versus intravenous. *Kidney Int (Suppl)* 1999;69:S61-S66.
- Macdougall IC. Quality of life and anemia: the nephrology experience. *Semin Oncol* 1998;25(3 Suppl 7):39-42.
- Schreiber S, Wedel S. Diagnosis and treatment of anemia in inflammatory bowel disease. *Inflammatory Bowel Diseases* 1997;3:204-16.
- Ponka P, Lok CN. The transferrin receptor: role in health and disease. *Int J Biochem Cell Biol* 1999;31:1111-37.
- Shih YJ, Baynes RD, Hudson BG, Flowers CH, Skikne BS, Cook JD. Serum transferrin receptor is a truncated form of tissue receptor. *J Biol Chem* 1990;265:19077-81.
- Beguín Y, Huebers HA, Josephson B, Finch CA. Transferrin receptors in rat plasma. *Proc Natl Acad Sci U S A* 1988;85:637-40.
- Kohgo Y, Niitsu Y, Kondo H, Kato J, Tsushima N, Sasaki K, et al. Serum transferrin receptor as a new index of erythropoiesis. *Blood* 1987;70:1955-8.
- Skikne BS, Flowers CH, Cook JD. Serum transferrin receptor: a quantitative measure of tissue iron deficiency. *Blood* 1990;75:1870-6.
- Weiss G. Iron and anemia of chronic disease. *Kidney Int (Suppl)* 1999;69:S12-S17.
- Punnonen K, Irjala K, Rajamaki A. Serum transferrin receptor and its ratio to serum ferritin in the diagnosis of iron deficiency. *Blood* 1997;89:1052-7.
- Klausner RD, Rouault TA, Harford JB. Regulating the fate of mRNA: the control of cellular iron metabolism. *Cell* 1993;72:19-28.
- Ponka P. Cellular iron metabolism. *Kidney Int (Suppl)* 1999;69:S2-S11.
- Hentze MW, Kuhn LC. Molecular control of vertebrate iron metabolism: mRNA-based regulatory circuits operated by iron, nitric oxide, and oxidative stress. *Proc Natl Acad Sci U S A* 1996;93:8175-82.
- Hansen TM, Hansen NE, Birgens HS, Holund B, Lorenzen I. Serum ferritin and the assessment of iron deficiency in rheumatoid arthritis. *Scand J Rheumatol* 1983;12:353-9.
- Thomson AB, Brust R, Ali MA, Mant MJ, Valberg LS. Iron deficiency in inflammatory bowel disease. Diagnostic efficacy of serum ferritin. *Am J Dig Dis* 1978;23:705-9.
- Weiss G, Wachter H, Fuchs D. Linkage of cell-mediated immunity to iron metabolism. *Immunol Today* 1995;16:495-500.
- Pantopoulos K, Weiss G, Hentze MW. Nitric oxide and oxidative stress (H<sub>2</sub>O<sub>2</sub>) control mammalian iron metabolism by different pathways. *Mol Cell Biol* 1996;16:3781-8.
- Child JA, Brozovic B, Dyer NH, Mollin DL, Dawson AM. The diagnosis of iron deficiency in patients with Crohn's disease. *Gut* 1973;14:642-8.
- Bartels U, Pedersen NS, Jarnum S. Iron absorption and serum ferritin in chronic inflammatory bowel disease. *Scand J Gastroenterol* 1978;13:649-56.
- Macdougall IC, Cavill I, Hulme B, et al. Detection of functional iron deficiency during erythropoietin treatment: a new approach. *BMJ* 1992;304:225-6.
- Cartwright GE. The anemia of chronic disorders. *Semin Hematol* 1966;3:351-75.
- Means RTJ, Krantz SB. Progress in understanding the pathogenesis of the anemia of chronic disease. *Blood* 1992;80:1639-47.
- Means RT, Jr. Advances in the anemia of chronic disease. *Int J Hematol* 1999;70:7-12.
- Means RTJ, Dessypris EN, Krantz SB. Inhibition of human erythroid colony-forming units by interleukin-1 is mediated by gamma interferon. *J Cell Physiol* 1992;150:59-64.
- Faquin WC, Schneider TJ, Goldberg MA. Effect of inflammatory cytokines on hypoxia-induced erythropoietin production. *Blood* 1992;79:1987-94.
- Means RTJ, Krantz SB. Inhibition of human erythroid colony-forming units by gamma interferon can be corrected by recombinant human erythropoietin. *Blood* 1991;78:2564-7.
- Reinisch W, Gasche C, Tillinger W, et al. Clinical relevance of serum interleukin-6 in Crohn's disease: single point measurements, therapy monitoring, and prediction of clinical relapse. *Am J Gastroenterol* 1999;94:2156-64.
- Horina JH, Petritsch W, Schmid CR, et al. Treatment of anemia in inflammatory bowel disease with recombinant human erythropoietin: results in three patients. *Gastroenterology* 1993;104:1828-31.
- Lin FK, Suggs S, Lin CH, et al. Cloning and expression of the human erythropoietin gene. *Proc Natl Acad Sci U S A* 1985;82:7580-4.
- Lee-Huang S. Cloning and expression of human erythropoietin cDNA in *Escherichia coli*. *Proc Natl Acad Sci U S A* 1984;81:2708-12.
- Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of end-stage renal disease with recombinant human erythropoietin. Results of a combined phase I and II clinical trial. *N Engl J Med* 1987;316:73-8.
- Ludwig H, Fritz E, Kotzmann H, Hocker P, Gisslinger H, Barnas U. Erythropoietin treatment of anemia associated with multiple myeloma. *N Engl J Med* 1990;322:1693-9.
- Pincus T, Olsen NJ, Russell JJ, et al. Multicenter study of recombinant human erythropoietin in correction of anemia in rheumatoid arthritis. *Am J Med* 1990;89:161-8.
- Tilbrook PA, Klinken SP. The erythropoietin receptor. *Int J Biochem Cell Biol* 1999;31:1001-5.
- Leitgeb C, Pecherstorfer M, Fritz E, Ludwig H. Quality of life in chronic anemia of cancer during treatment with recombinant human erythropoietin. *Cancer* 1994;73:2535-42.
- Gasche C, Dejaco C, Waldhoer T, et al. Intravenous iron and erythropoietin for anemia associated with Crohn disease. A randomized, controlled trial. *Ann Intern Med* 1997;126:782-7.
- Bruner AB, Joffe A, Duggan AK, Casella JF, Brandt J. Randomised study of cognitive effects of iron supplementation in non-anemic iron-deficient adolescent girls. *Lancet* 1996;348:992-6.
- Brown WS, Marsh JT, Wolcott D, et al. Cognitive function, mood and P3 latency: effects of the amelioration of anemia in dialysis patients. *Neuropsychologia* 1991;29:35-45.
- Grimm G, Stockenhuber F, Schneeweiss B, Madl C, Zeitlhofer J, Schneider B. Improvement of brain function in hemodialysis patients treated with erythropoietin. *Kidney Int* 1990;38:480-6.
- Babbs CF. Oxygen radicals in ulcerative colitis. *Free Radic Biol Med* 1992;13:169-81.
- Gordeuk VR, Brittenham GM, Bravo J, Hughes MA, Keating LJ. Prevention of iron deficiency with carbonyl iron in female blood donors. *Transfusion* 1990;30:239-45.
- Schreiber S, Howaldt S, Schnoor M, et al. Recombinant erythro-

- poietin for the treatment of anemia in inflammatory bowel disease. *N Engl J Med* 1996;334:619–23.
44. Geisser P, Baer M, Schaub E. Structure/histotoxicity relationship of parenteral iron preparations [German]. *Arzneimittelforschung* 1992;42:1439–52.
  45. Zanen AL, Adriaansen HJ, van Bommel EF, Posthuma R, Th de Jong GM. “Oversaturation” of transferrin after intravenous ferric gluconate (Ferrlecit) in haemodialysis patients. *Nephrol Dial Transplant* 1996;11:820–4.
  46. Nyvad O, Danielsen H, Madsen S. Intravenous iron-sucrose complex to reduce epoetin demand in dialysis patients [Letter]. *Lancet* 1994;344:1305–6.
  47. Mercuriali F, Gualtieri G, Sinigaglia L, et al. Use of recombinant human erythropoietin to assist autologous blood donation by anemic rheumatoid arthritis patients undergoing major orthopedic surgery. *Transfusion* 1994;34:501–6.
  48. Mercuriali F, Zanella A, Barosi G, et al. Use of erythropoietin to increase the volume of autologous blood donated by orthopedic patients. *Transfusion* 1993;33:55–60.
  49. Sunder-Plassmann G, Horl WH. Safety of intravenous injection of iron saccharate in haemodialysis patients. *Nephrol Dial Transplant* 1996;11:1797–1802.
  50. Gasche C, Dejaco C, Reinisch W, et al. Sequential treatment of anemia in ulcerative colitis with intravenous iron and erythropoietin. *Digestion* 1999;60:262–7.
  51. 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;132:155–9.