Gastroenterologist-Lead Management of Iron Deficiency Anemia in Inflammatory Bowel Disease Is Effective, Safe, and May Increase Quality of Life

Christopher L. Coe, MD,* Matthew H. Meyers, MD,* Dawn B. Beaulieu, MD,* Elizabeth Scoville, MD, MSC1,* David A. Schwartz, MD, FACP,* Sara N. Horst, MD, MPH,* and Robin L. Dalal, MD*

Background: The effectiveness and safety of gastroenterologist (GI)-lead treatment of iron deficiency anemia (IDA) in inflammatory bowel disease (IBD) have not been well-studied.

Methods: A retrospective chart review of patients with IBD, IDA, and evidence of treatment with iron at a tertiary IBD center was conducted.

Results: In 351 patients, hemoglobin and quality of life scores increased significantly after treatment with iron. Twelve of 341 patients treated with intravenous iron had an adverse effect. Twenty-seven patients required a hematology referral.

Conclusion: GIs should consider treating patients with IBD and IDA with intravenous iron as it is safe and effective.

INTRODUCTION

Inflammatory bowel disease (IBD) includes Crohn’s disease (CD), ulcerative colitis (UC), and indeterminate colitis. The hallmark of these chronic disorders is periodic flares of autoimmune-driven inflammation of the luminal gastrointestinal tract. Multiple extraintestinal manifestations (EIMs) further complicate the care of patients with IBD. These include skin, joint, and eye involvement1, 2; depression and anxiety; and nutrient deficiencies.3, 4 These EIMs can require additional subspecialist referrals, appointments, and treatments for IBD patients.

Of the EIMs of IBD, anemia (most commonly defined using the World Health Organization’s definition of a hemoglobin less than 12 g/dL in women and 13 g/dL in men5) is among the most common. Prevalence estimates for anemia in this population vary widely depending on the definition of anemia used and whether inpatients or outpatients were assessed. Indeed, a 2014 meta-analysis of 15 studies by Wilson et al5 noted a range from 8.8% to 73.7%. A large (n = 2192) systematic review by Filmann et al6 from the same year (but not included in Wilson’s analysis) noted a prevalence rate of 24%. In this study, 57% of these anemic patients were iron deficient, suggesting that about 14% had iron deficiency anemia (IDA). In a more recent cohort of 2666 Swiss patients in 2018, Madanchi et al7 found that 19.6% and 21.6% of CD and UC patients had IDA, respectively. Although the exact prevalence of anemia in IBD is unknown, it is higher than in the general population, which was recently estimated to be 5.6% in the United States.8

Generally, iron deficiency occurs when more iron is lost than is consumed in the diet. In IBD, increased intestinal blood loss from inflammatory lesions can lead to a negative iron balance.9, 10 Although iron absorption has historically been thought to be preserved in most patients with IBD,11 newer evidence suggests that impaired transluminal absorption during times of increased disease activity may also play a role.12 As has been previously well-reviewed,10 increased hepcidin levels...
when systemic inflammation is high decrease the dietary iron absorption. Dietary iron intake has been shown to be lower in patients with CD, further exacerbating iron deficiency. Medication side effects and cobalamin and folate deficiency likely play less important roles in the development of anemia in this population.

Anemia has been shown to decrease quality of life (QoL). In a recent Korean study of more than 30,000 subjects, anemia was found to significantly reduce mobility and the ability to perform usual activities. This leads to significantly reduced scores on a survey measuring health-related QoL. QoL is a measure that encompasses physical and psychosocial impairments. There are various disease-specific surveys used to measure QoL in IBD. The Inflammatory Bowel Disease Questionnaire and its shorter version, the Short Inflammatory Bowel Disease Questionnaire (SIBDQ) are IBD-specific patient questionnaires that allow for consistent measurement and documentation over time. We hypothesized that gastroenterologist (GI)-lead treatment of IDA in IBD patients would be safe and effective and, when combined with treatment of the underlying disorder, would increase QoL as measured by the SIBDQ.

**MATERIALS AND METHODS**

In this retrospective review, the medical records of patients aged 18 or older treated at a tertiary care IBD center between October 2012 and October 2017 were evaluated for the presence of both IBD and IDA. IDA was defined based on a hemoglobin concentration of less than 12 g/dL for women or less than 13 g/dL for men and ferritin less than 100 μg/L or a transferrin saturation of less than 20 mg/dL. IBD type, disease location, and disease phenotype were determined based on in-clinic documentation. Patients with CD were classified as either having small bowel only, large bowel only, small bowel and large bowel, pan-gut (any of the former in addition to having duodenal, gastric, or esophageal involvement), or perianal disease only. Inflammation of surgical pouches was classified as small bowel disease. Patients with CD were further classified as having either perianal or fistulizing phenotype, stricturing disease phenotype, or neither (inflammatory phenotype). Patients with UC were classified based on the presence of proctitis only, left-sided colitis only, or pancolitis. IBD patients with indeterminate colitis were not included given they are rarely encountered and their diagnosis tends to change frequently throughout their course.

Patients were included if their IDA was addressed by their GI (or, if inpatient, the consulting GI and primary team) and was treated with supplementation, either orally or with intravenous (IV) iron. Most commonly, iron sucrose (Venofer; American Regent, Shirley, NY) 200 mg weekly for 5 weeks or ferric carboxymaltose (Injextafer; American Regent) 750 mg weekly for 2 weeks is used in our center, although precise dosing is clinician and context dependent. Ferumoxytol (Feraheme; AMAG Pharmaceuticals, Waltham, MA) is used rarely in our center, and iron dextran (Infed; Allergan USA, Madison, NJ) is used rarely in the community. This center does not have a fixed protocol for iron supplementation, but IV iron is preferred.

Records of patients who had IDA were excluded if comorbid conditions also associated with anemia were present. These included malignancies, bleeding from a recent procedure, hematologic disorders such as thalassemia or myelodysplasia, chronic kidney disease, menorrhagia, and significant hemorrhoidal bleeding. Records of patients who had IDA but were not treated with iron supplementation or who were treated but did not have a posttreatment IBD center clinic visit within 6 months of treatment were also excluded. Patients who were to have received iron therapy but did not were excluded. Patients who began iron therapy but did not complete the prescribed course were included.

We compared QoL measures and hemoglobin levels at pretreatment with those from posttreatment clinic visits. The SIBDQ was used as a marker of QoL. The Harvey-Bradshaw Index (HBI) and simple clinical colitis activity index (SCCAI) were used for markers of disease activity in UC and CD, respectively. The presence or absence of endoscopic disease, iron levels, ferritin levels, transferrin saturation, C-reactive protein (CRP) level, recent hospitalizations, and any changes to medications were also noted if available. If IV iron was used, we searched the medical record for any evidence of an adverse reaction. Differences between pre- and posttreatment visit indices were tested for significance using a paired t-test.

**RESULTS**

The electronic medical records of 2327 patients who were seen in our IBD center were manually assessed. About 351 anemic patients with IBD (249 patients with CD, 102 patients with UC) were included. Most (62%) of patients were female. The median body mass index was in the overweight range (25). Ten percent of subjects used tobacco products and 22% were prescribed narcotics (Table 1).

Median disease duration was 7 years, with an interquartile range (IQR) of 3–15. Of the 249 patients with CD, 46% had both small and large bowel disease, 6% had upper gastrointestinal tract involvement, and 51% had fistulizing or perianal disease. Most (60%) of the 102 patients with UC had pancolitis. Endoscopy records were available for 223 CD patients and 94 UC patients, and 79% of the included IBD patients had active endoscopic disease within the 6 months before the diagnosis of IDA. About 27% were hospitalized for a flare within the preceding 6 months. About 26% of included patients were taking oral steroids at the time of diagnosis of IDA, and 60% were prescribed a biologic medication (Table 2).

Seventy-five patients (22%) had another EIM besides anemia. Eleven percent had a history of IBD-associated arthropathy, 5% of erythema nodosum, 5% of iritis or uveitis, 1% of pyoderma gangrenosum, and 2% of primary sclerosing...
cholangitis (PSC). Except for PSC, patients with CD had more EIMs (Table 2).

Of the patients evaluated, over 90% (341) were treated with IV preparations of iron. About 189 patients received iron sucrose, 139 patients received ferric carboxymaltose, 5 patients received feomxytol, and 2 received iron dextran. Six received an unknown formulation of IV iron. One of 4 GIs either wrote the prescriptions for iron supplementation or sent a recommendation for iron supplementation to the patient’s primary physician or local GI.

Adverse effects of IV iron therapy were reported in 12 instances (3.5%). Seven of these occurred in patients who received ferric carboxymaltose, 3 in patients who received iron sucrose, one in a patient who received ferumoxytol, and one in a patient who received iron dextran. In 4 of these, the adverse effect was pruritis and urticaria. Another 4 patients reported chest pain or indigestion during the infusion. One had swelling of the arm through which iron was being administered, and another had tingling of the extremities. One had an episode of presyncope and another had an episode of syncope. Only one patient (with arm swelling) required an emergency room visit; the cause of her swelling was thought to be due to an infiltrated IV. Eight of these patients went on to receive further IV iron supplementation in the future, although with a different formulation and infused at a slower rate. One patient is scheduled to receive an infusion but has not yet as of writing. In patients who received IV iron again, there was no report of a second adverse reaction.

The median time between pretreatment and posttreatment labs was 8 weeks (IQR 5–12), and the mean time was 10 weeks. Two-hundred and thirty-three patients had other changes in therapy. Of 4 GIs either wrote the prescriptions for iron supplementation or sent a recommendation for iron supplementation to the patient’s primary physician or local GI.

Pretreatment hemoglobin levels were available for all patients with CD, were in their 30s, overweight, and female. About 10% of included patients used tobacco products, and 22% were prescribed narcotics. n, number of patients for whom data was available; CD, Crohn’s disease; UC, ulcerative colitis.

Patients and posttreatment iron available for 183 subjects. Among 342 subjects. Pretreatment iron values were available for 345 patients and posttreatment iron available for 183 subjects. Among all participants with IBD, median hemoglobin values increased from 10.7 (IQR 9.6–11.3) to 12 g/dL (IQR 11–13) after treatment with iron (P < 0.001). Median iron levels increased from 22 (IQR 16–30) to 44 mcg/dL (IQR 28–82) (P < 0.001). Median ferritin levels increased from 11 (IQR 6–20) to 49 ng/mL (IQR 18–120) (P < 0.001). When separated by disease type, changes in hemoglobin, iron, and ferritin values remained significant with P ≤ 0.001. Median transferrin saturations increased from 7% (IQR 5–10) to 18% (IQR 11–27), but these changes only approached statistical significance (P = 0.052) (Table 3). More than half (53%) of patients evaluated required re-treatment for IDA.

SIBDQ scores were available for 336 subjects. Among patients with CD, median SIBDQ improved from 48 (IQR 36–58) to 54 (IQR 41–61) after treatment with iron (P < 0.001). Among patients with UC, SIBDQ improved from 46 (IQR 34–59) to 58 (IQR 44–64) (P < 0.001) (Table 4).

Pretreatment disease activity scores were available for 335 patients and posttreatment scores were available for 336 patients. Disease activity trended toward improvement according to HBI (CD) and SCAI (UC) but did not meet statistical significance. CRP decreased from a median of 5.7 (IQR 1.7–15.9) to 3.1 (IQR 0.9–12.0) (P < 0.005) (Table 4).

Twenty-seven included subjects (8%) had an outpatient hematologist. Of these, 8 were referred for reasons other than anemia (7 for thrombosis, concern for hypercoagulability, or management of anticoagulation and one for leukopenia). Three patients with IDA expressed a preference for hematology referral. One patient was referred by their primary internist for the management of mild IDA. Five others had long-standing anemia predating referral to our IBD center and were referred to hematology by other physicians. The remaining 10 patients were referred by their primary GI. Six of these were referred for persistent iron deficiency despite good control of luminal disease and concern for an alternative cause of anemia. Three were referred due to a lack of improvement in hemoglobin or iron parameters despite treatment. One was referred for evaluation by a hematologist before treatment with IV iron after reporting a history of anaphylaxis to IV iron.

**DISCUSSION**

Our data show a significant improvement in QoL as measured by SIBDQ scores after treatment with iron.
### TABLE 2. Disease Characteristics of Evaluated Patients by Disease Type

| Disease Type | Disease Location | Phenotype | Disease Duration (years) | Other Extraintestinal Manifestations | Steroid Prescription | Biologic Prescription | Endoscopic Activity | Prior Surgery for IBD | Hospitalization for Flare Within Past 6 Months |
|--------------|------------------|-----------|--------------------------|--------------------------------------|----------------------|-----------------------|---------------------|-------------------|---------------------------------------------|
| CD           | Small bowel: 73 (29%) | Stricturing: 51 (21%) | 38 | Arthritis: 33 (13%) | 21% | 62% | 75% (n = 223) | 57% | 29% |
|              | Large bowel: 42 (17%) | Perianal/ Fistulizing: 120 (51%) | ~ | EN: 18 (7%) | | | | | |
|              | Small and large bowel: Pan-gut: 15 (6%) | Perianal only: 4 (2%) | | PG: 4 (2%) | | | | | |
|              |                  |            |                           | PSC: 3 (1%) | | | | | |
|              |                  |            |                           | Iritis/Uveitis: 17 (7%) | | | | | |
| UC           | Prolific: 7 (7%) | ~ | 4 | Arthritis: 5 (5%) | 37% | 55% | 89% (n = 94) | 7% | 24% |
|              | Left sided: 34 (33%) | | | EN: 1 (1%) | | | | | |
|              | Pancolitis: 61 (60%) | | | PG: 0 | | | | | |
|              | Pan-gut: 15 (6%) | Perianal only: 4 (2%) | | PSC: 4 (4%) | | | | | |
|              |                  |            |                           | Iritis/Uveitis: 1 (1%) | | | | | |
| Combined     | ~ | ~ | 3 | Arthritis: 38 (11%) | 26% | 60% | 79% | 43% | 27% |
|              |                  |            |                           | EN: 19 (5%) | | | | | |
|              |                  |            |                           | PG: 4 (1%) | | | | | |
|              |                  |            |                           | PSC: 7 (2%) | | | | | |
|              |                  |            |                           | Iritis/Uveitis: 18 (5%) | | | | | |

For disease location, pan-gut includes patients with upper gastrointestinal disease, and patients are only counted once. Most patients had active endoscopic disease and more than a quarter of included patients were on steroids and had been hospitalized within the past month. About half of patients with CD had perianal or fistulizing disease. *B* represents the lower quartile, *A*, the median, and the upper quartile *C*. If *n* is the number of patients for whom endoscopic data were available; EN, erythema nodosum; PG, pyoderma gangrenosum; PSC, primary sclerosing cholangitis.
supplementation. Although it has been previously shown that the treatment of IDA in IBD improves QoL in both children and adults, our data add to the existing knowledge in important ways. To our knowledge, this is the largest retrospective study to date that was specifically designed to assess the impact of GI-led treatment of IDA in IBD on QoL in a real-world, clinical setting.

In evaluating the efficacy of a fixed-dose carboxymaltose regimen for the treatment of anemia in IBD, Eustatiev et al conducted a large (n = 485) randomized-controlled trial. However, they included only patients in remission or with mild to moderate disease based on the Crohn’s Disease Severity Index (CDAI) or Colitis Activity Index (CAI). We included patients with severe disease; 79% of our patients had active endoscopic activity at the time of iron supplementation and greater than 25% were hospitalized for their IBD in the preceding 6 months. Furthermore, in our study, median baseline CD activity as measured by HBI was 6 (IQR 3–10), greater than the cutoff typically used to indicate remission (<5) and equivalent to a CDAI score of approximately 188 (Table 3). We do note, however, that the median baseline SCCAI score of our UC patients was 4.5 (IQR 2.0–10), just below the typical cutoff of greater than 5 to indicate active disease (Table 3). It is possible that our UC patients had lower disease activity than our CD patients, although when endoscopy records were available they indicated endoscopic activity was present in 89% of our UC patients (Table 1).

Our study is also unique in that it suggests that GI-led management of IDA in a real-world setting can improve QoL when coupled with the treatment of the underlying disease. Eustatiev et al only assessed QoL responses to a controlled, standardized carboxymaltose regimen or a calculated-dose iron sucrose regimen. Likewise, Stein et al limited their prospective study to ferric carboxymaltose. In a similar prospective study, Gisbert et al only assessed patients treated with iron sucrose. Wells et al's small (n = 50) study showing improvement in QoL after treatment of IV iron was similarly limited to iron sucrose. As our study included patients dosed with any form and amount of iron, the results apply more directly to a real-world setting, where insurance and tolerability issues often drive physician choice of IV iron preparation.

Importantly, in the present study, we were unable to control for other potential causes of improved QoL between baseline and posttreatment follow-up. During each clinic visit, a multidisciplinary team including a mental health specialist and dietician meet the patients and provide recommendations. Furthermore, 233 patients changed medications between the initial and follow-up visits, and more than half of these changes involved biologic therapy, the cornerstone of treatment. These changes likely contributed to the decrease in CRP and an increase in QoL scores observed between pre- and posttreatment visits.
The majority of participants were treated with IV iron supplementation. Although there was no fixed protocol for supplementation in this center, oral iron was generally avoided due to concern for an increase in GI-related side effects. This concern is supported by available literature; a 2016 meta-analysis by Bonovas et al. found a treatment discontinuation rate of 10.9% and a statistically significant increase in reports of abdominal pain for patients receiving oral iron when compared to those treated with IV iron.

Importantly, anemia did improve in most patients, and therapy with IV iron was safe. Only 12 (3.5%) of patients treated with IV iron reported an adverse reaction, and most of these were mild; 9 of the 12 patients who experienced reactions went on to receive further infusions through the IBD center, although with steroid or antihistamine premedication, a different formulation, and a slower infusion rate. Notably, however, not all patients received their infusion at our center, so it is possible that some details regarding the presence and type of adverse reactions are incorrect or missing. Overall, these findings comport with the results of a 2015 meta-analysis of 103 trials examining the safety of IV iron prescriptions, which found that life-threatening reactions such as anaphylaxis are extremely rare, particularly with newer iron formulations and when iron dextran is avoided.

To our knowledge, this is the first study to measure the incidence of hematology referrals among patients with IBD. Our findings indicate that in most cases, a referral is not necessary and that the primary GI can treat this EIM of IBD. This lessens the burden on a patient population who already must travel for infusions, laboratory studies, and frequent visits with their GI. However, the persistence of IDA despite good control of IBD or a history of intolerance to IV iron should prompt further evaluation and may warrant a hematology referral.

CONCLUSION

Treating IDA and the underlying disease in patients with IBD improves QoL and can be done effectively and safely by the primary GI. The GI treating patients with IBD should have a low threshold to treat their iron-deficient patients with IV iron supplementation. Outside referral to a hematologist need not be pursued in most cases.

DATA AVAILABILITY

Data exists in a secure online suppository (RedCap) that includes basic patient information (demographics) and collected laboratory and clinical values. A de-identified export can be made available upon request.

REFERENCES

1. Vavricka SR, Brun L, Ballabeni P, et al. Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. Am J Gastroenterol. 2011;106:110–119.
2. Vavricka SR, Schoepfer A, Scharf M, et al. Extraintestinal manifestations of inflammatory bowel disease. Inflamm Bowel Dis. 2015;21:1982–1992.
3. Kurina LM, Goldacre MJ, Yeates D, et al. Depression and anxiety in people with inflammatory bowel disease. J Epidemiol Community Health. 2001;55: 723–729.
4. Madanchi M, Fagagnini S, Fournier N, et al.; Swiss IBD Cohort Study Group. The relevance of vitamin and iron deficiency in patients with inflammatory bowel diseases in patients of the Swiss IBD cohort. Inflamm Bowel Dis. 2018;24: 1768–1779.
5. Gasche C, Lomer MC, Cavill I, et al. Iron, anaemia, and inflammatory bowel diseases. Gut. 2004;53:1190–1197.
6. World Health Organization. Nutritional Anaemias: Tools for Effective Prevention and Control. Geneva: World Health Organization; 2017:7. https://apps.who.int/iris/bitstream/handle/10665/25942/9789241513067-eng.pdf?sequence=1
7. Wilson A, Reyes E, O’fman J. Prevalence and outcomes of anemia in inflammatory bowel disease: a systematic review of the literature. Am J Med. 2004;116(Suppl 7A):445–498.
8. Filman N, Rey J, Schneeweiss S, et al. Prevalence of anemia in inflammatory bowel diseases in European countries: a systematic review and individual patient data meta-analysis. Inflamm Bowel Dis. 2014;20:936–945.
9. Le CH. The prevalence of anemia and moderate/severe anemia in the US population (NHANES 2003–2012). PLoS One. 2016;11:e0166635.
10. Nielsen OH, Soendergaard C, Vinkier ME, et al. Rational management of iron-deficiency anaemia in inflammatory bowel disease. Nutrients. 2018;10(1). https://www.mdpi.com/2072-6643/10/1/82/htm