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Iron treatment and inflammatory bowel disease: What happens in real practice?☆

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Abstract

Background and aims: Iron deficiency anaemia (IDA), the most common extra-intestinal complication of inflammatory bowel disease (IBD), negatively impacts quality of life. We audited the recent practice of anaemia treatment in an unselected IBD population.
Methods: A questionnaire was distributed to adult IBD outpatients in a university hospital to assess the form and frequency of iron prescribed, duration of use, side effects, and completion of therapy. The efficacy of treatment was determined by the resolution of anaemia and change in haemoglobin from baseline.
Results: Of 87 IBD patients (60 patients with Crohn's disease, 25 with ulcerative colitis, 2 with microscopic colitis), 85 received various dosing regimens of iron tablets; 15 patients also received IV iron. Side effects were reported in 43 (51%) patients, with no clear relationship to dose prescribed and 26 (32%) patients were unable to complete the intended course. Only 36 (42%) patients completed the course of oral iron without side effects and in these patients, haemoglobin normalised in about 30%. Their median haemoglobin change was 12.5 (5.3–23.5) g/l. The median duration of treatment in those without side effects was 4.5 months, and in those with adverse effects was 2 months. Only one adverse effect was reported for IV iron.
Conclusions: Treatment with oral iron results in failure to control anaemia in 2 out of 3 IBD patients, which is likely in part to be due to the side effects reported by over half of patients. Patients failing to tolerate or adequately respond to therapy should be offered alternative treatment.

1. Introduction

Anaemia in IBD has a reported prevalence of between 6 and 74%,[1,2] yet historically has received little attention from gastroenterologists.[3] The aetiology of anaemia in IBD is multifactorial, frequently the result of both iron deficiency anaemia (IDA) and anaemia of chronic disease,[4,5,6] with rarer causes such as drug induced anaemia and B12/folate

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deficiency contributing to the complexity of this disease.[7] Anaemia has a significant detrimental impact on the quality of life of IBD patients, and in the majority of patients reduced haemoglobin is directly associated with physical and mental impairments.[2,8] Observational studies of iron replacement demonstrate a positive correlation between an increase in haemoglobin (Hb) level and quality of life questionnaire scores.[9,10]

According to guidelines,[11] anaemia in IBD should be treated in line with WHO guidance, iron supplementation aiming for a post-treatment Hb of 130 g/l in men and 120 g/l in women.[12] Iron is most commonly supplemented using tablets as this modality is cheap and convenient. However iron tablets frequently cause gastrointestinal side effects,[13] which limits tolerability and consequent adherence to this treatment. Furthermore, as iron absorption in the gut is carefully controlled,[14] large amounts of non-absorbed iron in the lumen of the gastrointestinal tract can result in oxidative stress and inflammation in the gut.[15,16] In the setting of randomised controlled trials, oral iron tablets seem to perform well in patients with IDA relating to IBD.[17] However, there is very little 'real life' data on iron use and tolerability in IBD patients in a clinical setting outside of formal trials. The aim of this study is to explore the use and tolerability of oral iron supplementation by IBD patients being treated in the community.

2. Methods

This was a retrospective study using a questionnaire distributed to adult IBD outpatients over an 8 week period at a tertiary referral IBD centre, Queen Elizabeth Hospital, Birmingham, UK. Information was gathered concerning patient demographics, the disease, form of iron prescribed, start date of treatment, frequency of dose, duration of use, side effects, concomitant use of immunomodulatory drugs and completion of the prescribed course of iron treatment. All patients included in the study had used oral or intravenous iron; none had been on erythropoiesis stimulating agents. Hence the history of oral iron use was captured in patients treated over the past 20 years, focussing on the most recent course of treatment prescribed. The electronic records of the patients were reviewed using the Queen Elizabeth Hospital Birmingham Trust electronic records and prescribing systems to ensure the accuracy of diagnosis and to follow Hb response to treatment, where available. The concurrent use of immunomodulators (including azathioprine, methotrexate, 6-mercaptopurine, infliximab and cyclosporin) was also documented.

Efficacy of oral iron therapy was measured by the median change in Hb from baseline and resolution of anaemia to normal reference ranges according to the WHO classification.[12] Both Hb change and duration of therapy are quoted as median (25th, 75th percentile). Statistical analysis was performed using PASW Statistics 18 (SPSS Inc., Chicago, Illinois). Comparisons were performed using Fisher's exact test for nominal data, Kendall's tau-b for ordinal data and the Mann–Whitney test for interval data. The study was registered with Queen Elizabeth Hospital Birmingham audit department (audit code CAB-03930-11).

3. Results

All 87 IBD patients surveyed (60 patients with Crohn's disease, 25 with ulcerative colitis (UC), 2 with microscopic

Table 1 Patients' demographics, IBD type, side effects, duration and efficacy of oral iron.

	All patients	Crohn's disease	Ulcerative colitis
Patient			
Patient number	87	60	25
Female	53 (61%)	38 (63%)	14 (56%)
Mean age in years (range)	42 (17–84)	40 (17–84)	46 (17–78)
Immunomodulatory drugs	50 (57%)	35 (58%)	14 (56%)
Patients on oral iron	85 (98%)	60 (100%)	23 (92%)
Patients on IV iron	17 (20%)	13 (22%)	4 (16%)
Frequency dosing of oral iron/day			
Once	25 (29%)	17 (28%)	8 (35%)
Two to three times	57 (67%)	41 (68%)	14 (61%)
Four and above	3 (4%)	2 (3%)	1 (4%)
Side effects to oral iron	43 (51%)	29 (48%)	12 (52%)
Constipation	16 (19%)	11 (18%)	4 (17%)
Abdominal pain	16 (19%)	12 (20%)	3 (13%)
Nausea	17 (20%)	11 (18%)	5 (22%)
Diarrhoea	15 (18%)	8 (13%)	5 (22%)
Median duration in months (25–75% quartiles)	3 (1–12)	3 (1–12)	3 (2–14)
Completion of oral iron	55/81 (68%)	36/56 (64%)	18/23 (78%)
Median Hb change g/l (25–75% quartiles)	6 (−1–20)	7 (3–20)	4 (0–16)
Resolution of Hb to normal reference range	16/55 (29%)	9/39 (23%)	6/15 (40%)

colitis) had received iron therapy. The mean age of the patients was 42. There were 53 women and 34 men, and immunomodulators were prescribed in 50 (57%) patients. Eighty-five (98%) patients received oral iron therapy (67 patients received ferrous sulphate, 15 received ferrous fumarate and 3 received ferrous gluconate). Seventeen (20%) patients received parenteral iron; only 2 patients received IV iron only. Various dosing regimes using iron tablets were described, with 25 (29%) patients taking iron once daily, 57 (67%) patients taking two or three tablets daily, and 3 (4%) patients taking four or more tablets daily.

Side effects were reported by 43 (51%) of the patients on iron tablets: constipation, abdominal pain, nausea and diarrhoea being reported with similar frequency (18–20% of patients). In total, 55 (68%) patients were able to complete their prescribed course of iron therapy. For those patients on oral iron, the median Hb change was 7 (3–20) g/l in Crohn's patients and 4 (0–16) g/l in UC patients. Haemoglobin normalised in only 16 patients, which represents about a third (29%) of those for whom efficacy data was available.

Table 1 summarises the demographic and clinical characteristics of the 87 patients. With regard to the effect of age on side effects we found that in our cohort, patients over the age of 40 years (63%) were more likely to suffer side effects compared to those under the this age (37%) ($p = 0.030$).

Table 2 compares the dosing regimens, treatment duration and therapeutic outcomes in patients who had adverse effects on iron tablets compared to those who did not. There were no significant differences in dosing frequency between the two groups ($p = 1.000$). The median duration of treatment in those with side effects was 2 months (1–10), whilst in patients without side effects it was 4.5 months (2–12) ($p = 0.052$). Treatment was significantly more effective in those without adverse effects with a median increase in Hb of 12.0 (5.8–23.5) g/l compared to 4.0 (−1.8–12.8) g/l in those who reported side effects ($p = 0.028$). Only one adverse effect to iron dextran infusion was reported in one of the 17 patients on IV iron. This was an anaphylactoid allergic reaction.

4. Discussion

In this retrospective audit of recent treatment we found that iron tablets were mainly used to correct IDA in our IBD patients, consistent with widespread practice across Europe.[18] Our studies demonstrated that patients take very varied daily doses of iron tablets in practice. The traditional dosing regimen of 150–200 mg of elemental iron daily is equivalent to three tablets of ferrous sulphate and has been associated with gastrointestinal side effects in up to 20% of patients in historical trial data.[19] Indeed the maximum absorptive capacity of the duodenum is limited to 10–20 mg per day and this can be readily saturated [20]; therefore patients are routinely overdosed.

In randomised controlled trials the prevalence of side effects on oral iron has been shown to be dose dependent,[21,22] patients receiving 15 mg daily having very few side effects in comparison to those on 150 mg daily, with no change in efficacy.[23] In this context, the observation in the current study that side effects related to iron tablets have no clear relationship to daily dosing frequency seems surprising. We speculate that this may relate to the large amounts of iron in a single tablet, variable recall of adherence, or the exacerbation of underlying gastrointestinal symptoms in this particularly vulnerable cohort of patients. Those patients with side effects tended to take their tablets for approximately half the duration and to be less likely to have a resolution of their anaemia compared to those who tolerated iron tablets without side effects. Despite this, the median duration of treatment was prolonged, even patients with gastrointestinal side effects persisted for two months with their tablets.

Previous studies addressing tolerance and efficacy of oral iron in IBD patients have shown a similar side effect profile and efficacy to that of non-IBD patients with no significant difference between Crohn's disease and UC groups,[24,25] in concordance with our study. A prospective open label study included 33 IBD patients,[25] in which 200 mg ferrous sulphate was given three times daily for 4 weeks and a discontinuation

Table 2 Frequency, duration and efficacy of oral iron in those with and without side effects.

	No side effects	Side effects	p-Value *
Number of patients on oral iron	42 (49%)	43 (51%)	
Duration and efficacy of oral iron course in all patients			
Frequency dosing of oral iron/day			1.000
Once	12 (29%)	13 (30%)	
Two to three times	29 (69%)	28 (65%)	
Four and above	1 (2%)	2 (5%)	
Duration of oral iron in months (25–75% quartile)	4.5 (2–12)	2 (1–10)	0.052
Median Hb change/g/l (25–75% quartile)	12.0 (5.8–23.5)	4.0 (−1.8–12.8)	0.028
Patients with Hb resolution to reference range	9/25 (36%)	7/30 (23%)	0.377
Patients completing course of oral iron			
Number of patients completing course	36/39 (92%)	19/42 (45%)	<0.0001
Duration of oral iron in months (25–75% quartile)	4.5 (2–12)	3 (2–14.5)	0.967
Median Hb change/g/l (25–75% quartile)	12.5 (5.3–23.5)	4.5 (0.3–19.5)	0.315
Patients with Hb resolution to reference range	8/19 (42%)	4/13 (31%)	0.713

* p-Value < 0.05 is considered to be statistically significant.

rate of 21% was reported. However, of the 65 patients invited into their study, 12% declined due to previous poor tolerability of iron and 15% were lost to follow-up; if these patients were included, 35–44% of patients would have potentially reported iron intolerance. This supports the contention that intolerance of iron may be much higher outside of clinical trials.

IV iron has been advocated by many as a better tolerated, more effective form of replacement therapy with a faster and more prolonged response rate, supported in a recent meta-analysis[26] of the following studies.[17,27,28] One large multicentre study of 91 patients over a 20 week period demonstrated that oral iron was significantly less effective in increasing Hb by 20 g/l (42% versus 66%, p = 0.07) and tolerance was found to be poor over this prolonged time period, resulting in dose reduction in 23% and discontinuation in 25% of individuals,[17] similar to our study findings. IV iron therapy in comparison has been shown to be well tolerated and safe,[29] and life-threatening adverse reactions such as anaphylaxis are relatively rare in all formulations other than those in which iron is linked to high molecular weight iron dextran.[30] Among our patients one out of 17 suffered a hypersensitivity reaction. As there is , as yet, limited data from clinical trials using the newer iron formulations (linked to smaller sugars), the MHRA advocates caution in their use and exhorts physicians to report any side effects.[31]

The retrospective nature of the study and reliance on patient recall may introduce bias, as those who have had intolerance to oral iron are more likely to recollect side effects and cessation of therapy. Moreover, there may be confounding by indication, in that those patients having side effects may also have more severe inflammatory bowel disease or other co-morbidities. Though our patient number is greater than that reported in most clinical trials studying efficacy and the tolerance of oral iron, the numbers are still small, making analysis of sub-group data less reliable. Despite this, our results are comparable to those in observational cohorts, consistent with real-life experience, as previously discussed.

In summary, although oral iron is a cheap and convenient treatment for IDA, our pragmatic study revealed that treatment most commonly results in failure, seen in 2 out of 3 IBD patients. This is likely in part to be due to the gastrointestinal side effects that over half of our patients experienced, yet for many the treatment course of oral iron was long. We propose that when iron tablets are considered for patients with IBD, there should be a pre-determined duration of treatment, with a dose of no more than 100 mg elemental iron daily (one tablet). There should be a defined target end point Hb and early review of patients with regard to adherence and adverse effects. Those who fail to tolerate or do not respond adequately should consider an alternative form of iron therapy, such as IV iron.

Conflict of interest

TI has received lecture fees from Vifor Pharma in the past and is currently Chief Investigator of a trial of oral iron in IBD. All other authors have no actual or potential conflict of interest.

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SL carried out the data collection and drafted the final manuscript. FB carried out data collection and data analysis. TI conceived the study, participated in the design and critically revised the manuscript. PN performed the statistical analysis. NB assisted with data analysis and reviewed the final manuscript. All authors read and approved the final manuscript.

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