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Article *in* International Journal of Clinical Pharmacy · May 2020

DOI: 10.1007/s11096-020-01044-x

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RESEARCH ARTICLE

Treatment of iron deficiency anemia with liposomal iron in inflammatory bowel disease: efficacy and impact on quality of life

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Received: 19 October 2019 / Accepted: 22 April 2020

Abstract

Background Anemia is a clinical condition frequently seen in patients with inflammatory bowel disease, which is responsible for a significant loss of quality of life. *Objective* To assess the efficacy and safety of using oral liposomal iron to treat iron deficiency anemia in inflammatory bowel disease patients, as well as assess the impact of this treatment on psychometric scores. *Methods* Patients with inactive/mildly active inflammatory bowel disease were screened for anemia in this interventional pilot study conducted from November 2016 to March 2018. Patients with mild anemia were treated with oral liposomal iron for 8 weeks. *Main outcome measure* The primary endpoint of the study was the response to liposomal oral iron therapy. Treatment response was defined as patients who achieved a hemoglobin increase of ≥ 1 g/dL and/or hemoglobin normalization by the 8th week of treatment. *Results* Out of 200 screened patients, 40 (20%) had anemia. Of the 21 patients who completed treatment, 13 (62%) responded to oral liposomal iron replacement therapy (mean increases of hemoglobin from 11.4 to 12.6 g/dL). The transferrin saturation index increased by an average of 10.2 ($p = 0.006$) and the quality of life by 26.3 ($p < 0.0001$). There was also a mean reduction of 9.2 in the perception of fatigue ($p < 0.0001$). *Conclusion* Treatment with oral liposomal iron is effective in improving mild iron deficiency anemia and quality of life, as well as in decreasing fatigue in patients with inactive or mildly active inflammatory bowel disease.

Keywords Anemia · Crohn's disease · Fatigue · Inflammatory bowel disease · Oral iron therapy · Quality of life · Ulcerative colitis

Impacts on practice

- Prompt diagnosis and timely therapy for iron deficiency anemia (IDA) leads to an improvement in quality of life and prevention of potential damage.
- Treatment with liposomal iron, a new formulation of oral iron, is well tolerated and effective in improving mild IDA and quality of life in IBD patients with inactive or mildly active disease.

Introduction

Inflammatory bowel diseases (IBD) are multisystem conditions that entail substantial personal cost for many patients due to the unpredictable fluctuating course of symptoms, absences

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11096-020-01044-x) contains supplementary material, which is available to authorized users.

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Published online: 05 May 2020

from work, and continuous need of expensive drugs, surgeries, and multidisciplinary care [1].

Iron deficiency anemia (IDA) is one of the most common IBD complications [2]. The IDA mechanism in IBD is multifactorial and includes increased blood loss due to gastrointestinal inflammation, as well as decreased iron absorption, loss of appetite, and block of intestinal iron uptake [3]. Importantly, symptomatic anemia can contribute to patients' poor quality of life [4]. In addition, anemia is a significant risk factor for hospitalization, and increased mortality in IBD patients [5].

According to a systematic review, it is estimated that the mean prevalence of anemia in IBD is approximately 20% in outpatients and 68% in hospitalized patients [6]. It is well known that the correction of anemia has a beneficial impact on patients' quality of life. Therefore, screening, diagnosing and managing anemia should be part of the efforts to improve the quality of the care provided to all IBD patients.

Oral ferrous iron formulations such as ferrous sulfate, ferrous gluconate and ferrous fumarate have been traditionally used to treat mild IDA in several conditions, including IBD [7, 8]. Unfortunately, although the oral iron treatment is cheaper and convenient, it is not always well tolerated due to gastrointestinal side effects [9, 10]. Moreover, a large portion of the oral ferrous iron salts administered to patients is not absorbed and subsequently undergoes oxidation in the gut lumen and/or mucosa, fact that leads to the generation of reactive oxygen species (ROS) which may damage the intestinal epithelium [11–14]. However, clinical studies have found that patients treated with oral iron showed no significant increase in IBD activity [15, 16]. Nonetheless, it is worth emphasizing that even when the therapy with oral traditional iron formulations is well tolerated, a portion of IBD patients do not respond to it and require intravenous iron treatment [15, 16].

The liposomal iron, a preparation of ferric pyrophosphate carried within a phospholipid and sucrose esters of fatty acid membrane, is a new generation of oral iron, which shows high gastrointestinal absorption and high bioavailability [17, 18]. In comparison with others oral traditional iron preparations, the liposomal iron seems to be a promising new iron replacement strategy in IDA patients, due to the low incidence of side effects [19]. This pilot study was designed to assess both the efficacy and safety of the oral liposomal iron in treating mild anemia in inactive or mildly active IBD patients as well as the impact of this treatment on psychometric scores.

Aim of the study

The primary objective of this study is to evaluate the response rate to liposomal oral iron treatment as a new oral therapy to treat IDA in patients with IBD in remission or with mildly active disease.

Secondary objectives are to assess changes in ferritin concentration and transferrin saturation (TfS) throughout the 8th week; the impact of oral iron treatment on quality of life, fatigue scores, changes in disease activity, adherence to therapy, and the safety and tolerability of treatment.

Ethics approval

The study protocol was defined in accordance with the Declaration of Helsinki and approved by our Institutional Ethics Committee. All patients signed a free and informed consent form before being included in the study. They could withdraw their consent or discontinue their participation at any time. This trial was registered on NCT02760940 in 07-08th-2016.

Method

This is an open-label pilot study conducted from November 2016 to March 2018, in adult outpatients with IBD attended in the Inflammatory Bowel Disease Center at the University Hospital of Federal University of the Juiz de Fora, Brazil. The IBD diagnosis was based on clinical, radiological, endoscopic and histopathological criteria generally accepted for ulcerative colitis (UC) or Crohn disease (CD) [20].

Participants

Patients with IBD were eligible if they were age $\geq$ 18 years and $\leq$ 65 years with inactive or mildly active disease and had a diagnosis of mild anemia. Mild anemia was defined as hemoglobin between 11.0–11.9 g/dL in women and 11.0–12.9 g/L in men [21, 22]. Iron deficiency was defined by serum ferritin < 30 µg/L in patients without clinical or biochemical evidence of active IBD; in the presence of inflammation, a serum ferritin $\leq$ 100 µg/L was consistent with iron deficiency [22].

Patients were not included in the study whenever any of the following conditions were found in the initial screening: patients younger than 18 or older than 65 years, moderately-to-severely active IBD, other pre-existing chronic disease (e.g. liver disease, kidney failure, clinically significant pulmonary or heart diseases), systemic infection in the previous 3 months, current history of any type of malignancy (except for skin cancer), alcohol abuse (daily alcohol consumption above 20 g), drug addiction, previous gastrectomy, history of total colectomy or extensive intestinal resection (> 100 cm), hemoglobin < 11.0 g/dL, folate, or vitamin B12 deficiency, or replacement therapy using iron, folic acid or vitamin B12 in the previous 6 months. Pregnant women or nursing mothers were also excluded.

Measurements and outcomes

Baseline characteristics

At entry, the eligibility criteria were assessed, and patients' medical history recorded. The following relevant patient data was gathered in the initial assessment: age, gender, smoking status. Disease-associated variables evaluated were type of IBD, location, and phenotype (for CD), according to the Montreal classification [23]. CD activity was measured through the Harvey-Bradshaw Index (HBI). A HBI below 5 was considered as clinical remission, and scores between 5 and 7 were considered mildly active disease [24, 25]. The disease activity for UC patients was determined according to the Truelove and Witt's criteria [26]. Thus, clinical remission was defined as ≤ 2 stools/day with no blood and/or pus, and no systemic symptoms; mild activity was defined as up to 4 stools/day, with or without blood and no systemic manifestation [26]. Biological activity was defined by C-reactive protein (CRP) level above 5 mg/L.

Disease-specific quality of life

The disease-specific quality of life (QOL) was assessed at baseline and at the 8th week using a country-specific, validated version of the Inflammatory Bowel Disease Questionnaire (IBDQ). The cut-off points used in the IBDQ interpretation are based on a previous study [24]: ≥ 200 (excellent), between 151 and 199 (good), between 101 and 150 (regular), and ≤ 100 (poor) [27].

Fatigue measurement

The participants were instructed to answer the fatigue questionnaire (Chalder Fatigue Scale) at the time they were included in the study and 8 weeks after the beginning of the treatment. The Chalder Fatigue Scale is a British instrument used to measure physical and mental fatigue and it has already been translated into Portuguese and validated in Brazil [28].

The questionnaire comprises 11 items related to the intensity of fatigue symptoms. The items were in bimodal scores. Items are rated on a 4-point Likert scale (0 = better than usual, 1 = no more than usual, 2 = worse than usual, 3 = much worse than usual), with higher scores indicating greater fatigue perception [28].

Hematological assessment

The participants were instructed to fast 8 h before the blood draw for routine analysis. Blood samples were collected from these patients in order to determine the following laboratory data: erythrogram, serum iron, ferritin, transferrin saturation (TfS), erythrocyte sedimentation rate (ESR) and quantitative CRP. Vitamin B12, and folate levels were measured to exclude patients with anemia caused by these deficiencies.

Intervention

After screening, the enrolled patients were treated with oral liposomal iron supplement (Fisiogen Ferrol®, Zambon) for 8 weeks. The replenishment was provided to the patients at the dose of two liposomal iron tablets per day (equivalent to 28 mg of liposomal iron). The patients were instructed to take the tablets at any time of the day, regardless of meals. They were monitored by telephone at weekly interval throughout the intervention phase in order to maximize their therapy adherence and check for the occurrence of side effects. Furthermore, the Truelove and Witt's criteria, as well as the HBI, were monitored to evaluate occasional IBD flares in UC and CD patients, respectively, during the follow-up (at the 4th and 8th treatment weeks).

After the first 4 treatment weeks, the patients returned and brought the remaining oral iron tablets in order to allow assessment of their adherence to the treatment regimen and to receive a oral liposomal iron refill to complete the 8 treatment weeks. High adherence to the therapy was defined as the proportion of patients taking at least 80% of their prescribed medication, while low adherence as less than 80% of prescribed doses taken [29].

Reassessment

The same instruments and hematological assessments performed at the entry were repeated at the end of the 8th treatment week with oral iron supplementation.

Outcome measurements

Primary endpoint

The primary endpoint of the study was the response rate to liposomal oral iron therapy in treating mild anemia in inactive or mildly active IBD patients. Treatment responders were defined as patients who achieved hemoglobin (Hb) increase of at least ≥ 1 g/dL and/or Hb normalization by the 8th treatment week. Hb normalization was defined as Hb values ≥ 12 g/dL for women or ≥ 13 g/dL for men [21].

Secondary endpoints

The secondary endpoints included changes in ferritin concentration and TfS percentage from the baseline to the 8th week; effects of the oral iron treatment on quality of life, and fatigue; changes in disease activity (assessed by HBI,

Truelove and Witt's criteria, and CRP); adherence to therapy and treatment safety and tolerability.

Safety and tolerability

Safety and tolerability were assessed based on adverse events (AEs) observed throughout the study and on routine hematological indices. Patients who developed Hb concentrations ≤ 9.0 g/dL and/or disease flare during the study were considered as presenting serious adverse events and were withdrawn from the study to receive standard medical treatment. Serum pregnancy tests were conducted in female patients and the use of concomitant medications was assessed in all patients at each clinical visit. Adverse effects such as abdominal pain, diarrhea, nausea or vomiting that precluded the use of medication based on investigator's opinion were considered as non-serious adverse events.

Results

Study population

A total of 200 patients with inactive or mildly active IBD (100 with UC and 100 with CD) underwent screening and anemia was detected in 40 (20%) patients. Among them, 11 were not eligible to participate in the process due to lack of interest, pregnancy, surgical intercurrence or underlying cardiac insufficiency. Eight (23%) patients were not enrolled because they presented evidence of moderately active CD or severe anemia.

As a result, 21 patients (14 female) were included, 15 patients (71.4%) with CD and 6 (28.6%) with UC. Baseline demographic and clinical characteristics are depicted in Table 1. The mean age was 41.3 ± 14.6 years (range 18–62 years). Approximately 19% presented previous intestinal resection, but none suffered from short-bowel syndrome.

One UC patient presented proctitis, 3 left-sided UC and 2 extensive UC. Ileocolon was the most frequent location of CD (40%) followed by colon (33.3%). For CD disease, 4 patients had non-stricturing non-penetrating disease (26.7%), 9 had stricturing CD (60%) while the 2 remaining patients had penetrating CD (13.3%). All recruited patients were undergoing treatment for IBD: 15 (71.4%) were on azathioprine, 3 (14.3%) were on glucocorticoides, 5 (23.8%) patients were on anti-TNF agents while 3 (14.3%) were on salicylates.

The mean Hb level was 11.4 g/dL at baseline, while the mean serum iron and ferritin were 59.1 mg/dL and 98.8 µg/L, respectively.

Table 1 Baseline demographic and clinical characteristics of patients

Characteristic	N (%)
Gender (M:F)	7 (33.3):14 (66.7)
Age (year)[a]	41.3 ± 14.6
Current smoker	1 (4.3)
Type of IBD (CD:UC)	15 (71.4): 6 (28.6)
Disease location	
CD—[L1/L2/L3]	4(26.7)/5 (33.3)/6 (40)
UC—[E1/E2/E3]	1 (16.7)/3 (50)/2(33.3)
Disease behavior (CD) [B1/B2/B3]	4 (26.7)/9 (60)/2 (13.3)
Disease duration (year)[a]	6.2 ± 2.3
Previous intestinal resection	4 (19)
IBD-specific treatment	
Glucocorticoides	3 (14.3)
Anti TNFα agents	5 (23.8)
Aminodalicylates	3 (14.3)
Azathioprine	15 (71.4)

UC ulcerative colitis, *CD* Crohn's disease, *L1* ileal, *L2* colonic, *L3* ileocolonic, *E1* ulcerative proctitis, *E2* left-sided UC, *E3* extensive UC (pancolitis), *B1* non-stricturing, non-penetrating, *B2* stricturing, *B3* penetrating

[a]Mean ± standard deviation

Treatment response

Thirteen of the 21 patients (61.9%) responded to oral liposomal iron replacement therapy (mean increases of Hb from 11.4 to 12.6 g/dL). Of these, 9 (69.2%) achieved Hb increase of at least ≥ 1 g/dL and 12 (92.3%) achieved Hb normalization by the 8th treatment week. In addition, there was a significant improvement in baseline serum iron (59.1 to 86.8 mg/L; $p = 0.005$) and TfS (20.1% to 30.4%; $p = 0.006$) values after treatment with oral liposomal iron, despite no significant difference in ferritin values (Table 2).

Disease-specific quality of life, fatigue, and disease activity

There was significant improvement in the IBDQ scores after the oral liposomal iron therapy for 8 weeks. The baseline IBDQ score for the cohort was 157 (± 37) with a mean increase in the score by 26.4 ($p < 0.001$) at week 8 compared to the baseline. In addition, we found a notable reduction in the perception of fatigue after 8 weeks of oral liposomal iron therapy compared to the baseline (30.9 vs. 21.6; $p < 0.001$; Table 2 and Table 3—supplementary material). There was a linear correlation between the increase in Hb levels and the improvement of QOL as evaluated by IBDQ ($r = 0.54$; $p = 0.01$; Fig. 1).

Following oral liposomal iron therapy, no change was seen in clinical disease activity ($p = 0.10$). In addition, CRP levels remained unchanged after treatment ($p = 0.98$).

Table 2 Outcomes after 8 weeks of treatment with oral liposomal iron

Variable	Baseline[a]	Week 8[a]	p value
Hemoglobin (g/dL)	11.4 ± 0.7	12.6 ± 1.3	0.003
Ferritin (µg/L)	98.8 ± 110.6	123.1 ± 126.7	0.25
Serum iron (mg/L)	59.1 ± 23.8	86.8 ± 34.4	0.005
TfS (%)	20.1 ± 10.1	30.4 ± 15.1	0.006
C-reactive protein (mg/L)	7.1 ± 6.7	7.1 ± 9.6	0.98
ESR (mm/h)	13 ± 8.7	12 ± 7.5	0.90
HBI score	2.7 ± 1.9	2 1 ± 1.5	0.55
Truelove e Witts[b]	2.5 ± 1.1	2.1 ± 1.3	0.85
Fatigue score	30.9 ± 8.7	21.6 ± 8.4	< 0.001
IBDQ score	157 ± 37	183.4 ± 37.8	< 0.001

TfS, *transferrin saturation;* ESR, erythrocyte sedimentation rate; HBI, Harvey-Bradshaw Index; IBDQ, Inflammatory Bowel Disease Questionnaire

[a]Mean ± standard deviation

[b]Reported by *number of unformed stools* passed daily

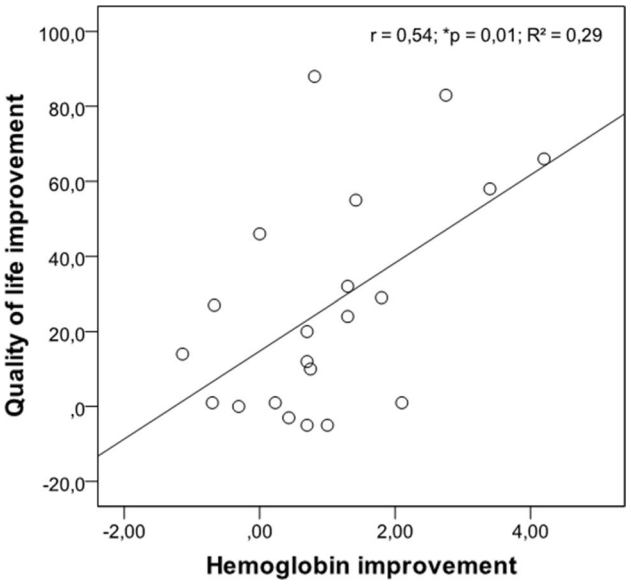

Fig. 1 Relationship between hemoglobin levels after treatment with oral liposomal iron and improvement in the perception of quality of life

Adherence to therapy, safety, and tolerability

The adherence rate for oral liposomal iron was 81%. When looking at compliance with treatment, only four patients took less than 80% of the prescribed capsules (missing more than eight capsules) by the end of treatment. No drug-attributed serious adverse events occurred. Also, no patient was withdrawn from the study or was lost to follow-up and no IBD flare was observed during the period of the study. Likewise, no non-serious adverse event that prevented the use of liposomal iron was reported.

Discussion

This pilot study showed that oral liposomal iron replacement therapy in inactive or mildly active IBD patients with mild IDA was efficient and well tolerated, with 62% (13 out 21) of patients achieving the primary endpoint, i.e. Hb increase of at least ≥ 1 g/dL or Hb normalization by the 8th treatment week. Moreover, we observed a significant improvement in baseline serum iron and TfS values after treatment. In addition, there was a reduction in the perception of fatigue and an increment disease specific QOL in the studied population which correlated with the enhancement of serum hemoglobin levels.

IDA affects 13–90% of IBD patients according to a recent series of studies [30, 31]. Traditional oral iron formulations in IBD patients may result in gastrointestinal side effects. Therefore, oral iron supplementation in IBD patients with IDA is challenging, and guidelines often recommend the use of intravenous iron formulations [6]. Such formulae are more expensive than oral iron and also necessitates venous access as well infusion monitoring due to possible hypersensitivity reactions [9, 16].

Nevertheless, initial clinical data in IBD patients suggest that oral iron formulations with improved tolerability, such as liposomal iron or ferric maltol, may represent a viable alternative to intravenous iron, at least for patients with mild-to-moderate IDA [32, 33]. The administration of oral liposomal iron appears to be a viable option to treat mild IDA, and even more so for individuals with IBD who often experience intolerance, worsening of gastrointestinal symptoms and lack of efficacy with other traditional oral iron salt formulations [19, 34].

The present study used liposomal iron replacement therapy for 8 weeks and observed a significant increase in Hb levels (mean increase: 11.4 to 12.6 g/dL), in IBD patients with correction of IDA in 62% of the total population. This finding is in agreement with a previous report [33] published only in abstract format that indicated that the Hb increased more in IBD patients presenting with IDA treated with liposomal iron than those treated with ferrous sulfate (62.5% vs. 33.3%, respectively). It is important to note that in our study there was no change in the ferritin level, probably because some patients with mildly active IBD already have normal baseline ferritin levels which could be attributed to the role of ferritin as an inflammatory protein. Moreover, in this pilot study, the patients were treated with oral liposomal iron for only 8 weeks, not enough time for the repletion of tissue ferritin while the recommended duration of oral iron therapy is commonly between 3 and 6 months [35].

We found a good tolerability and high adherence to therapy, which can clearly be seen, once all of the 21 (100%) completed the study, with 81% taking the entire prescribed regimen. Four patients, who took less than 80% of the prescribed therapy, reported forgetfulness as the reason for missing therapy. This finding is in accordance with those of Pisani and colleagues [19] that also observed good tolerability of liposomal iron in chronic kidney disease patients, with only minor side effects, such as constipation and diarrhea reported. Although the absence of cost associated with treatment could have played a role in the high adherence, we believe that it wasn't the main factor involved. We consider that high adherence to therapy was likely due mostly to the good tolerance of liposomal formulation as none of the patients presented with any adverse effects.

The ECCO (European Crohn's and Colitis Organization) recommends a dose no higher than 100 mg elemental iron per day for treatment of IBD patients with mild anemia. However, lower doses (15–30 mg daily) of traditional oral iron preparations have been effective and well tolerated in other patient populations (i.e., pregnancy and octogenarians) [36, 37]. To our knowledge, no study has evaluated the efficacy and safety of lower doses (between 15 and 30 mg daily) of traditional oral iron formulations for treatment of IBD patients with mild anemia. Of note, our pilot study is the first to assess the efficacy, adherence, and safety (incidence of adverse events) of low doses of oral liposomal iron for treating mild anemia in inactive or mildly active IBD patients. We are hopeful that future studies are carried out to compare low doses of both oral liposomal iron and traditional oral iron preparations for treatment of mild IDA in IBD patients.

It is hypothesized that the treatment of IDA with specific oral iron formulations may exacerbate the inflammatory process in IBD patients [13]. It has been shown that in IBD patients who take iron sulfate, ROS-mediated oxidative damage acts on a mucosa already damaged by the underlying disease, establishing a vicious cycle of further mucosal injury [11, 13]. So, we assessed changes in disease activity scores following oral liposomal iron therapy, and no change was seen either clinical disease activity nor serum CRP levels after treatment. This finding could be explained by the liposomal formulation which avoids iron interfacing with the intestinal mucosa since it is released by the liposome only once it reaches the hepatocyte through lymphatic circulation [38]. Therefore, thanks to the optimal bioavailability due to the specific mechanism of absorption, it is possible that free iron is not generated in the intestinal lumen, and ROS production is avoided. However, we did not measure the generation of ROS in our study.

As already reported in several studies, the presence of anemia correlates directly with both a worsening in patients' QOL and the perception of fatigue [39–42]. This study showed an improvement in the QOL following iron therapy in patients with IDA, which was linearly associated with increases in Hb levels. Importantly, a significant reduction in fatigue perception was noted. Fatigue is an important clinical issue in patients with IBD and may contribute to lower health-related QOL in this population [41, 42]. Thus, oral liposomal iron therapy in patients with IBD presenting with concomitant mild IDA and fatigue may be useful for mitigating complaints of fatigue in this setting.

The present study has some limitations. Firstly, it is a single-center pilot study with a small number of patients. Secondly, the iron preparation tested in the study contains a relatively low dose of elemental iron (28 mg) compared to traditional compounds, which may be a reason why the increase in Hb levels in our study was not pronounced. We can speculate that an increase in liposomal iron dosage may result in further increase in serum Hb levels. In addition, the short-term course of treatment could have affected the response, mainly regarding the replenishment of iron stores. Thirdly, as the study population comprises only six patients with UC, we were unable to draw any conclusions about the difference in efficacy of iron oral therapy in the two disease states (UC *versus* CD). Finally, it could be interesting to compare oral liposomal iron therapy with both traditional oral iron preparations and intravenous iron for the treatment of mild IDA in IBD patients.

Conclusion

In summary, this pilot study provides data supporting the therapeutic use of oral liposomal iron for treating mild IDA in IBD and paves the way for future studies involving larger IBD populations utilizing higher doses of this drug and longer follow-up, to further evaluate the role of oral liposomal iron in treating quiescent or mildly active IBD patients presenting mild IDA.

Acknowledgements The Zambon Pharmaceutical Laboratory has made a substantial contribution by donating the complete treatment to patients. José Otávio do Amaral Correa and Sandra Neves dos Santos provided very valuable assistance by performing the laboratory analysis.

Funding No specific funding was received.

Conflicts of interest There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work which could have influenced its outcome.

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