Digestive and Liver Disease 56 (2024) 1483–1489

Contents lists available at ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Alimentary Tract

Follow-up evaluation and management of anemia in inflammatory bowel disease: A study by the Italian Group for Inflammatory Bowel Diseases (IG-IBD)

Gaetano Bergamaschi[a,*], Fabiana Castiglione[b], Renata D'Incà[c], Marco Astegiano[d], Walter Fries[e], Monica Milla[f], Carolina Ciacci[g], Fernando Rizzello[h], Simone Saibeni[i], Rachele Ciccocioppo[j], Ambrogio Orlando[k], Fabrizio Bossa[l], Mariabeatrice Principi[m], Piero Vernia[n], Chiara Ricci[o], Maria L. Scribano[p,q], Giorgia Bodini[r], Dario Mazzucco[s], Gabrio Bassotti[t], Gabriele Riegler[u], Andrea Buda[v], Matteo Neri[w], Flavio Caprioli[x], Fabio Monica[y], Aldo Manca[z], Erica Villa[aa], Gionata Fiorino[ab,ac], Nicola Aronico[a], Marco V. Lenti[a], Caterina Mengoli[a], Anna Testa[b], Maurizio Vecchi[x], Catherine Klersy[ad], Antonio Di Sabatino[a,*], on behalf of the RIDART I investigators[1]

[a] *Medicina Generale I, Fondazione IRCCS Policlinico San Matteo e Università di Pavia, 27100 Pavia, Italy*
[b] *Gastroenterology, Department of Clinical Medicine and Surgery, University Federico II of Naples, 80138 Naples, Italy*
[c] *Inflammatory Bowel disease Unit- AO-University of Padua, 35122 Padova, Italy*
[d] *Gastroenterology and Digestive Endoscopy Unit, "Città della Salute e della Scienza" Hospital, 10126 Torino, Italy*
[e] *Gastroenterology and Clinical Unit for inflammatory bowel diseases, Dept. of Clinical and Experimental Medicine; University of Messina, 98122 Messina, Italy*
[f] *Unità operativa complessa di Gastroenterologia clinica, Azienda ospedaliero universitaria Careggi- Firenze, 50134 Firenze, Italy*
[g] *Gastroenterology and Endoscopy Unit, AOU San Giovanni di Dio e Ruggi d'Aragona and University of Salerno, 84084 Salerno, Italy*
[h] *Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy*
[i] *Gastroenterology Unit, Rho Hospital, ASST Rhodense, 20017 Rho (MI), Italy*
[j] *Gastroenterology Unit, Department of Medicine, A.O.U.I. Policlinico G.B. Rossi & University of Verona, 37134 Verona, Italy*
[k] *Inflammatory Bowel Disease Unit, A.O.O.R. "Villa Sofia-Cervello", 90146 Palermo Italy*
[l] *Department of Gastroenterology and Endoscopy, Fondazione "Casa Sollievo della Sofferenza", IRCCS, 71013 San Giovanni Rotondo, Italy*
[m] *Gastroenterology Unit (D.E.T.O.), University of Bari, 70121 Bari, Italy*
[n] *Division of Gastroenterology, Department of Translational and Precision Medicine, "Sapienza" University of Rome and Umberto I Hospital, 00161 Rome, Italy*
[o] *Dept of Experimental and Clinical Science, University of Brescia, Gastroenterology Unit,Spedali Civili Hospital, 25123 Brescia. Italy*
[p] *Gastroenterology and Endoscopy Unit, Azienda Ospedaliera San Camillo-Forlanini, 00152 Rome, Italy*
[q] *Villa Stuart, Multi-Speciality Clinic, 00135 Rome, Italy*
[r] *Gastroenterology unit, Department of Internal medicine, Policlinico San Martino, Università di Genova, 16132 Genoa, Italy*
[s] *Gastroenterology Unit, ASL TO3, 10097 Rivoli, Torino, Italy*
[t] *Gastroenterology, Hepatology & Digestive Endoscopy Section, Department of Medicine & Surgery, University of Perugia and Perugia General Hospital, 06129 Perugia, Italy*
[u] *Unit of Gastroenterology - Reference Center for IBD - Second University of Naples, 80138 Naples, Italy*
[v] *Department of Gastrointestinal Oncological Surgery, Gastroenterology Unit, S. Maria del Prato Hospital, 30032 Feltre, Italy*
[w] *Department of Medicine and Ageing Sciences and Center for Advanced Studies and Technology (CAST), "G. d'Annunzio" University of Chieti-Pescara, 66013 Chieti, Italy*
[x] *Gastroenterology and Endoscopy Unit, Fondazione IRCCS Cà Granda, Ospedale Maggiore Policlinico and Università degli Studi di Milano, 20122 Milan, Italy*
[y] *Gastroenterology and Digestive Endoscopy Unit, Cattinara Academic Hospital, 34149 Trieste, Italy*
[z] *Department of Gastroenterology and Digestive Endoscopy, S. Croce e Carle Hospital, 12100 Cuneo, Italy*
[aa] *UC Gastroenterologia, Dipartimento di Specialità Mediche, Azienda Ospedaliera Universitaria di Modena, 41125 Modena, Italy*
[ab] *Department of Gastroenterology and Digestive Endoscopy, San Raffaele Hospital and Vita-Salute San Raffaele University, 20132 Milan, Italy*
[ac] *IBD Unit, San Camillo-Forlanini Hospital, 00152 Rome, Italy*
[ad] *Servizio di Epidemiologia Clinica & Biometria, Fondazione IRCCS Policlinico San Matteo, 27100 Pavia, Italy*

[*] Corresponding authors at: Fondazione IRCCS Policlinico San Matteo e Università di Pavia, Piazzale Golgi 19, 27100 Pavia, Italy
E-mail addresses: gaetanobergamaschi@gmail.com (G. Bergamaschi), a.disabatino@smatteo.pv.it (A. Di Sabatino).
[1] See Acknowledgments section.

https://doi.org/10.1016/j.dld.2024.01.176

ARTICLE INFO

Article history:
Received 21 November 2023
Accepted 4 January 2024
Available online 30 January 2024

Keywords:
Inflammatory bowel disease
Iron-deficiency anemia
Vitamin-deficiency anemia
Anemia therapy

ABSTRACT

Background: The RIDART I study found a 13.6% prevalence of anemia in Italian patients with inflammatory bowel disease (IBD); most cases were due to iron-deficiency anemia (IDA).
Aims: To evaluate changes in hemoglobin concentration during a 24-week follow-up of anemic patients with IBD.
Methods: Follow-up laboratory and clinical data were obtained from RIDART I study patients with anemia. Factors affecting hemoglobin concentration, the impact of anemia on fatigue and quality of life (QoL), and its relationship with treatment, disease activity and disease complications were investigated.
Results: Hemoglobin was 108 g/L at baseline, increased to 121 g/L at follow-up week 12 ($p < 0.001$) and then stabilized until week 24, but most patients remained anemic, with IDA, throughout the study. Hemoglobin improvement was greater in patients receiving either oral or parenteral iron supplementation. Following hemoglobin normalization, anemia relapse rate during follow-up was 30%. Oral iron did not cause disease reactivation. Lower follow-up hemoglobin was associated with a higher probability of having active disease, clinical complications, increased fatigue and reduced QoL.
Conclusions: In anemic patients with IBD, anemia represents a long-lasting problem, in most cases persisting for up to 24 weeks, with high relapse rate and a negative impact on fatigue and QoL.

1. Introduction

Anemia is one of the most common extraintestinal manifestations of inflammatory bowel diseases (IBD), with a prevalence ranging from 6% to 74% [1], and it is associated with reduced survival and poor quality of life (QoL) [2–4]. An individual patient meta-analysis, that included original European full-paper publications, found a 24% prevalence of anemia (95% CI 18 to 31%) in IBD [5]; on average, it was calculated that each patient with IBD spends almost 2 months every year in an anemic state [6]. Although inflammation is a frequent cause of IBD-associated anemia, most cases are due to iron deficiency (ID) and, to a lesser extent, vitamin B_{12} or folic acid deficiency, conditions that can be effectively treated by replacement therapy. Accordingly, scientific societies guidelines, reviews and position papers concerning the management of IBD suggest active treatment of iron-deficiency anemia (IDA) and of ID without anemia as a mean to improve QoL of patients with IBD [7–12]. In addition, anemia of IBD has a high relapse rate; strict monitoring of hemoglobin (Hb) values and iron status is, thus, mandatory after treatment of IDA with iron supplementation, even in patients who successfully respond to iron replacement therapy, and maintenance iron supplementation after initial treatment, or re-treatment are strongly recommended when anemia relapses or serum ferritin falls below 100 µg/l [8,13,14].

Recently we conducted an observational study, RIDART I (Clinical Burden of Anemia in IBD: Role of Iron Deficiency and Iron Replacement Therapy), on the prevalence, etiology and management of anemia in IBD; data on anemia prevalence and etiology showed that, in Italy, in an outpatient gastroenterological setting, approximately 13.6% (95% CI 12.7–14.6%) of adult individuals with IBD were anemic and ID, either isolated or in association with inflammation and/or vitamin deficiencies, contributes to over 80% of cases [15]. In addition, the study showed that up to 30% of IBD patients with IDA and 60% of those with vitamin deficiencies were not treated with supplementation of deficient factors, thus confirming previous reports demonstrating that most IBD patients with anemia are not tested for iron deficiency and a large proportion of those with documented IDA are left untreated [6,16,17]. Here we report the results of a follow-up analysis in which RIDART I patients with baseline anemia were investigated for Hb changes during a period lasting up to 24 weeks from enrollment. Factors affecting Hb concentration and the effects of anemia and its treatment on fatigue and QoL during follow-up were analyzed.

2. Patients and methods

2.1. Setting of the study and ethical statements

The RIDART I study is a multicenter, cross-sectional and prospective observational study on the prevalence of anemia in IBD. The study was promoted by the Italian Group for Inflammatory Bowel Diseases (IG-IBD), was approved by the institutional review boards of participating Centers (27 Italian tertiary IBD referral Centers), registered on ClinicalTrials.gov (NCT02872376) and was conducted following the principles of the Declaration of Helsinki. Participating patients provided written informed consent. Patients' data were entered, in a semi-anonymized format, in a secured database based on the REDCap platform at the coordinating institution (Pavia, Italy). Details on RIDART I design and results concerning the study primary objective have been reported [15].[15]

2.2. Study patients and anemia definitions

Given the observational nature of the study, patients were treated in each center by an expert IBD physician. Hence, the optimal treatments targeting IBD and anemia were decided as per current clinical practice. IBD outpatients, at least 18 years old and with anemia, were consecutively enrolled in the RIDART I study; clinical and laboratory data were obtained at baseline and during scheduled follow-up visits at weeks 4, 12 and 24 from enrollment. Follow-up evaluation included anamnesis, physical examination, blood tests and determination of disease activity using the Crohn disease (CD) activity index (CDAI) and the colitis activity index (CAI) for Crohn's disease and ulcerative colitis (UC), respectively [18,19]; active disease was characterized by a CDAI score > 150 in CD and a CAI score > 4 in UC. QoL was assessed using the Italian validated version of the Inflammatory Bowel Disease Questionnaire (IBDQ) score, with higher scores indicating better QoL [20]. Fatigue was determined by means of a visual analogue scale, with a range from 1 to 100, higher values indicating more severe fatigue. Disease extension and behavior were reported according to the Montreal classification [21,22], whereas anemia and its etiology were defined as described [15,23,24]. Anemia was characterized by Hb < 120 g/L in females and < 130 g/L in males; it was considered mild if Hb ≥ 110 g/L, moderate if Hb ≥ 80 g/L but < 110 g/L, severe if Hb < 80 g/L [23]. In IDA serum ferritin was < 30 µg/L; anemia of inflammation (AI) was identified by serum ferritin > 100 µg/L and

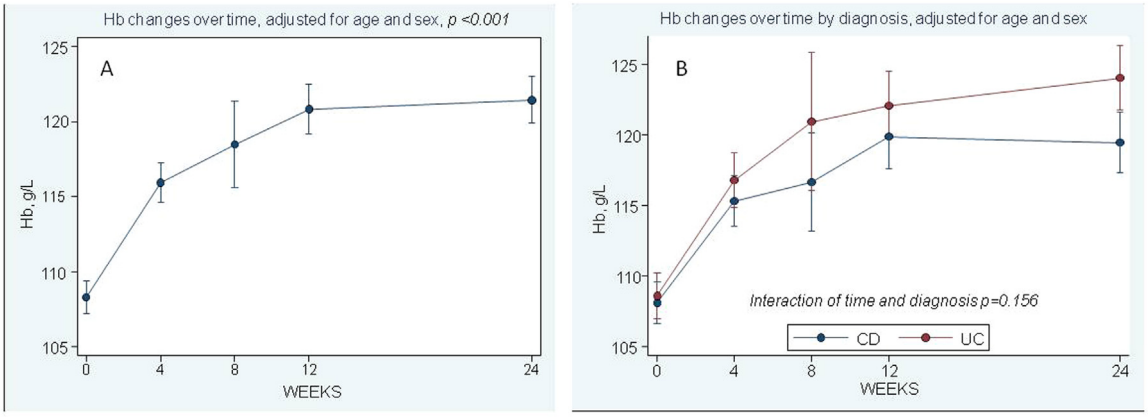

Fig. 1. Age- and sex-adjusted hemoglobin concentrations at different time points during the RIDART I study. Panel A shows Hb values in the total series of patients; panel B shows hemglobin in CD and UC patients. Hemoglobin is shown as means and 95% CI. CD, Crohn's disease; UC, ulcerative colitis.

transferrin saturation < 20%; the association of IDA and AI (InfI-IDA) was characterized by transferrin saturation < 20% and serum ferritin ≥ 30 but ≤ 100 µg/L [24,25]. Cut-off values for the diagnosis of vitamin deficiencies were serum vitamin B12 < 200 ng/L and folate < 2.0 µg/L. Renal function evaluation was based on determination of the estimated glomerular filtration rate (eGFR) using the new Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation [26].

2.3. Main outcomes and measures

Hb concentration, the prevalence of anemia as well as the proportion of patients who obtained Hb normalization or an elevation of Hb concentration ≥ 10 g/L or ≥ 20 g/L compared with baseline were determined during the follow-up of RIDART I patients (Hb normalization or an elevation ≥10 g/L or ≥ 20 g/L are usually considered as response criteria in studies on IDA treatment). Influence of type of anemia, disease activity and iron or vitamin supplementation on Hb concentration at different time points during the study was investigated. Changes in fatigue and QoL, development of clinical problems (requirement for hospital admissions, surgical procedures, unscheduled endoscopic examinations or appearance of new comorbidities) and their relations with Hb, treatment and disease activity were additionally evaluated.

2.4. Statistical analysis

Continuous data were described as medians and interquartile ranges (IQRs) or means and 95% confidence intervals (CI) as appropriate; categorical variables as counts and percentages. The association of continuous variables was assessed by means of the Spearman R test. Changes over time were analyzed using generalized linear regression models for repeated measures. Huber-White robust standard errors were computed to account for the lack of independence between outcomes. To compare groups over time a term of interaction of time and group was included in the models. Model assumptions were verified graphically using a residual-versus-fitted plot. All analyses were performed using the Stata software (release 18, StataCorp, College Station, TX, USA). A 2-sided *p*-value <0.05 was considered statistically significant. The Bonferroni correction was applied for post-hoc comparisons. No missing data imputation was performed.

This paper was written in accordance with the STROBE guidelines for quality assurance. The raw data of the study are not publicly available due to privacy restrictions, but can be shared by the corresponding author upon reasonable request.

3. Results

Of 737 patients with IBD and anemia enrolled in the RIDART I study, 537 had laboratory and clinical data available for analysis; the number of patients enrolled in each center and the number of patients treated with either oral or intravenous (iv) iron supplementation are shown in supplementary Table 1. Table 1 highlights the main characteristics of patients at different time points during the study. Age- and sex-adjusted Hb concentration increased from 108 g/L (95% CI 107–109 g/L) at week 0 to 121 g/L (95% CI 119–122 g/L) at week 12 and then stabilized until week 24 ($p < 0.001$, Fig. 1A). Serum ferritin and transferrin saturation also increased during follow-up, but most patients remained anemic throughout the study, with serum ferritin < 30 ng/mL and transferrin saturation < 20% at follow-up weeks 12 and 24 (Table 1). Only 6 patients required red blood cell transfusions.

Hb improved over time in both CD and UC (Fig. 1B); at week 24, however, improvement was greater in UC ($p = 0.037$). Similarly, more UC than CD patients achieved Hb normalization or a Hb increase ≥ 10 or 20 g/L within week 24 (supplementary Table 2). Considering the whole patient population, active disease at the baseline evaluation was characterized by lower Hb concentration than quiescent disease, but was not predictive of persistently lower Hb concentrations during follow-up (Fig. 2, panel A). However, at any follow-up time point, males and patients with quiescent disease maintained higher Hb concentrations than females and individuals with active disease, although Hb improvement was similar in active and quiescent disease as well as in female and male patients (Fig. 2, panels B and C); no gender-related differences were reported in the proportion of patients who attained Hb normalization or Hb elevation ≥ 10 or 20 g/L during follow-up (supplementary Table 2). Follow-up CRP was lower than the basal value but remained higher than the upper limit of normal (5 mg/L) in approximately 50% of cases (Table 1), and inverse correlations were found between follow-up CRP and the corresponding Hb values (supplementary Table 3). Baseline eGFR showed a weak positive correlation with Hb changes during follow-up (larger Hb improvement in subjects with higher eGFR).

Baseline Hb was lower in IDA than in InfIIDA, but Hb elevation during follow-up was greater in IDA compared with InfIIDA and AI (Fig. 3). Iron supplementation further improved Hb concentration, especially at later time points during the study; at week 24 Hb increased 18 g/L in iron treated patients (95% CI 15–20 g/L), but only 9 g/L (95% CI 6–12 g/L) in untreated patients ($p < 0.001$, Fig. 4A). Final Hb concentration was similar in patients treated with either iv or oral iron supplementation, but Hb elevation from baseline to weeks 12 and 24 was larger, though not statistically significant,

Table 1
Demographic and clinical characteristics of patients investigated at different time points in the RIDART I study.

Patients data	Study time points				*p*
	Baseline	FU week 4	FU week 12	FU week 24	
Females/males (female%)	280/257 (52)	190/193 (50)	165/178 (48)	159/172 (48)	0.574
Age, years	44 (31–58)	43 (30–58)	43 (30–58)	43 (30–58)	0.948
CD/UC, N (CD%)	306/233 (57)	217/166 (57)	191/152 (56)	189/142 (57)	0.984
Hb, g/L	108 (107–109)	116 (114–117)	121 (119–122)	121 (120–123)	< 0.001
Patients with anemia, *N* (%)	–	291 (75)	205 (59)	193 (58)	< 0.001
Hb normalization or ≥ 10 g/L Hb increase, *N* (%)	–	182 (47) 390	211 (60) 349	204 (61) 335	< 0.001
Hb normalization or ≥ 20 g/L Hb increase, *N* (%)	–	130 (33) 390	171 (49) 349	165 (49) 335	< 0.001
Active disease, *N* (%)	213 (40)	119 (31)	88 (25)	78 (24)	< 0.001
Anemia in quiescent disease, *N* (%)	–	182 (71)	136 (54)	134 (55)	< 0.001
Fatigue, score	50 (28–68)	32 (20–56)	30 (15–50)	30 (15–60)	< 0.001
IBDQ, score	166 (130–193)	175 (144–198)	173 (142–198)	178 (148–200)	< 0.001
Serum ferritin, ng/mL	12 (6–40)*	33 (11–154)*	26 (10–77)*	25 (10–64)*	< 0.001
Serum ferritin <30 ng/mL, *N* (%)	339 (71)	171 (47)	167 (53)	163 (55)	< 0.001
Transferrin saturation,%	7 (5–13)*	12 (7–20)*	12 (7–21)*	13 (8–20)*	< 0.001
Transferrin saturation <20%, *N* (%)	353 (88)	183 (72)	159 (73)	150 (75)	< 0.001
CRP, mg/L	7.0 (3.0–29.1)*	5.0 (2.5–24.2)*	5.0 (2.0–20.0)*	5.0 (2.5–17.6)*	0.008
CRP ≥5.0 mg/L, *N* (%)	305 (61)	184 (52)	165 (50)	167 (52)	0.003
eGFR, ml/min/1.73 m^2	106 (92–118)*	–	–	–	–

FU, follow-up; Hb, hemoglobin; CD, Crohn's disease; UC, ulcerative colitis; N, number of patients; IBDQ, Inflammatory Bowel Disease Questionnaire; CRP, C-reactive protein; NS, not significant. Values are reported as medians and interquartile ranges or numbers of patients and%. Continuous variables with normal distribution are shown as means and 95% CI; those with non-normal distribution* are reported as medians and IQR.

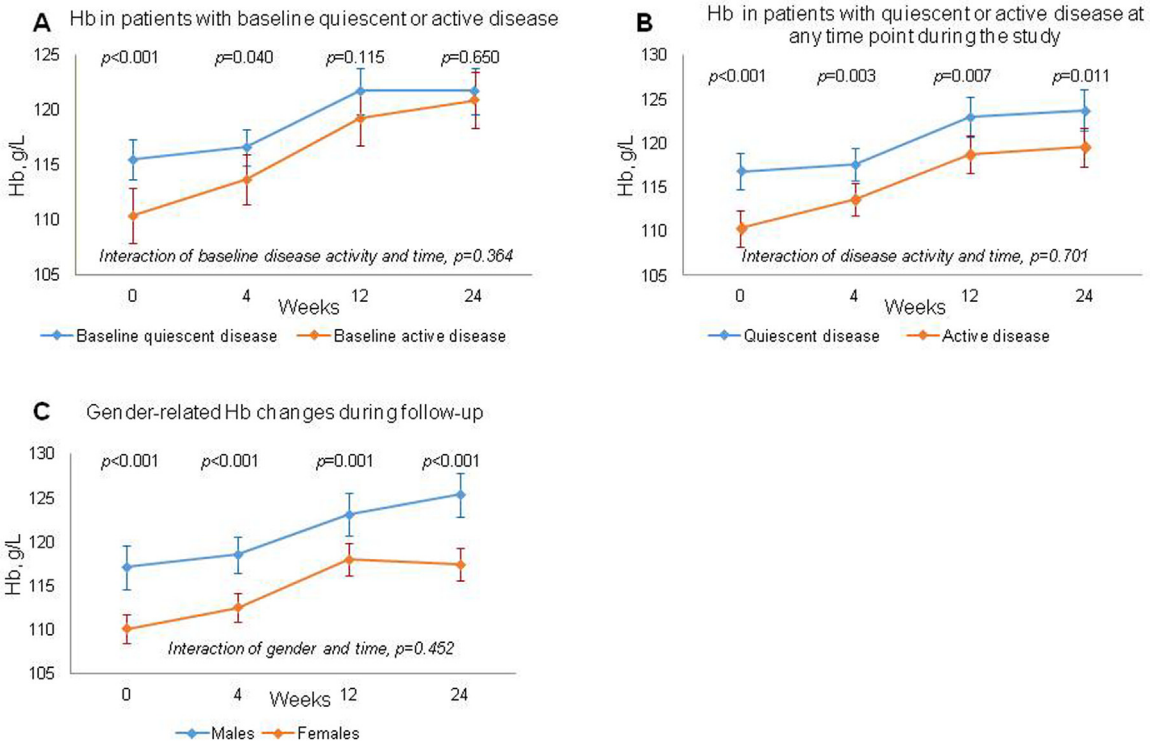

Fig. 2. Hemoglobin concentrations over time and influence of sex and disease activity. Panel A: hemoglobin in subjects with quiescent or with active disease at the baseline evaluation; panel B: hemoglobin in subjects with quiescent or with active disease at any time point during the study. Values are shown as means and 95% CI. Convergence of panel A curves at week 24 is explained by 53% to 56% of patients with time 0 active disease shifting to quiescent disease at follow-up weeks 12 and 24, and 10% to 12% of patients with time 0 quiescent disease progressing to active disease at the same time points. Hemoglobin concentrations are reported as means and 95% CI.

in the iv iron group (Fig. 4B). Patients treated with iv iron likely had more severe disease than those treated with oral iron; at the baseline evaluation, in fact, they had lower Hb, serum ferritin and transferrin saturation, more severe fatigue and, as far as CD patients are concerned, higher CDAI score (Fig. 4B and supplementary Table 4). In addition, individuals in the parenteral iron group were more likely to have active disease at week 0, though the difference with the oral iron group was not statistically significant, and more frequently underwent additional endoscopic examinations; no differences concerning other clinical and laboratory parameters were reported (supplementary Table 4). Treatment with oral iron did not increase the risk to develop active disease in the

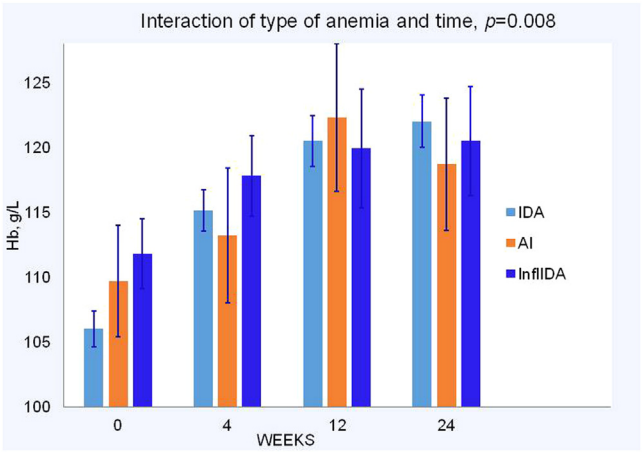

Fig. 3. Over time changes of hemoglobin in different types of anemia; changes were more pronounced in IDA. Values are reported as means and 95% CI. IDA, iron deficiency anemia, AI, anemia of inflammation; InfIIDA, anemia of inflammation associated with iron deficiency.

course of the study (supplementary Table 5). Vitamin B_{12} and/or folate were usually provided in association with iron supplementation, even in patients without ascertained vitamin deficiencies, and this obscured their effect on follow-up Hb. When patients with vitamin deficiencies were investigated in a separate analysis, vitamin supplementation was associated with a larger Hb elevation than no treatment; the difference, however, did not reach statistical significance due to the low number of cases (supplementary Figure 1A). Patients with relevant clinical problems during follow-up had lower Hb concentrations at weeks 0, 4 and 24 (supplementary Figure 1B), and this was essentially due to patients requiring at least one hospital admission in the course of the study (supplementary Table 6). Disease extension and behavior had no influence on follow-up Hb concentration (data not shown).

Among patients with Hb normalization at some point during the study, anemia relapsed in 16 of 76 cases between weeks 4 and 12 and in 43 of 141 within week 24. Relapse rate at week 24 was higher in females and patients with CD but was not influenced by age and disease activity. Relapse was usually associated with lower transferrin saturation, reduced QoL and increased fatigue (supplementary Table 7).

Quiescent disease and higher Hb concentrations were associated with less fatigue and better QoL at any time point during the study (supplementary Tables 8 and 9). Fatigue improved during follow-up (Table 1); improvement was not influenced by iron treatment (supplementary Figure 2A), but was greater in patients who received parenteral compared with oral iron supplementation ($p = 0.001$, supplementary Figure 2B). QoL slightly increased over time (Table 1), this being essentially due to the increasing proportion of patients whose disease became quiescent during follow-up (data not shown).

Subjects treated with systemic steroids during the study had lower baseline Hb than those treated with biologics, other immunosuppressors or no immune-modulating agents and were more likely to have active disease; during follow-up, however, differences between treatment groups lost statistical significance (supplementary Table 10).

4. Discussion

Anemia is a common health problem worldwide; it is associated with increased morbidity, mortality, years lived with disability and economic costs. Digestive system diseases contribute to a significant proportion of cases [27]. Data reported in the current work expand our previous findings on patients with anemia and IBD recruited in the RIDART I study [154]. Here we show that IBD-associated anemia usually improves during a follow-up period lasting up to 24 weeks, with Hb normalization or $a \geq 10$ g/L increase in over 50% of cases, but most patients remain anemic, with iron deficiency and some degree of inflammation (CRP above the upper limit of normal) throughout the period of observation. Initial analysis of RIDART I reported a 13.6% prevalence of anemia in IBD, indicating that each patient, in our series, has anemia for a mean of approximately 50 days each year [15]; current results suggest that in most cases anemia becomes a chronic problem that persists at least 6 months from diagnosis and negatively affects fatigue and QoL (supplementary Tables 7 and 8). These findings also confirm previous reports demonstrating that anemia in IBD has a high relapse rate, also in patients who successfully responded to iv iron replacement [13,14]; following Hb normalization, in fact, anemia relapsed in 30% of our patients within 12 to 20 weeks of follow-up.

As previously shown [28,29] active disease, together with elevated CRP and reduced baseline renal function, was one of the main determinants of fatigue and reduced QoL and a risk factor for persistent and relapsing anemia; the prevalence of anemia, however, remained greater than 50% also in subjects with quiescent

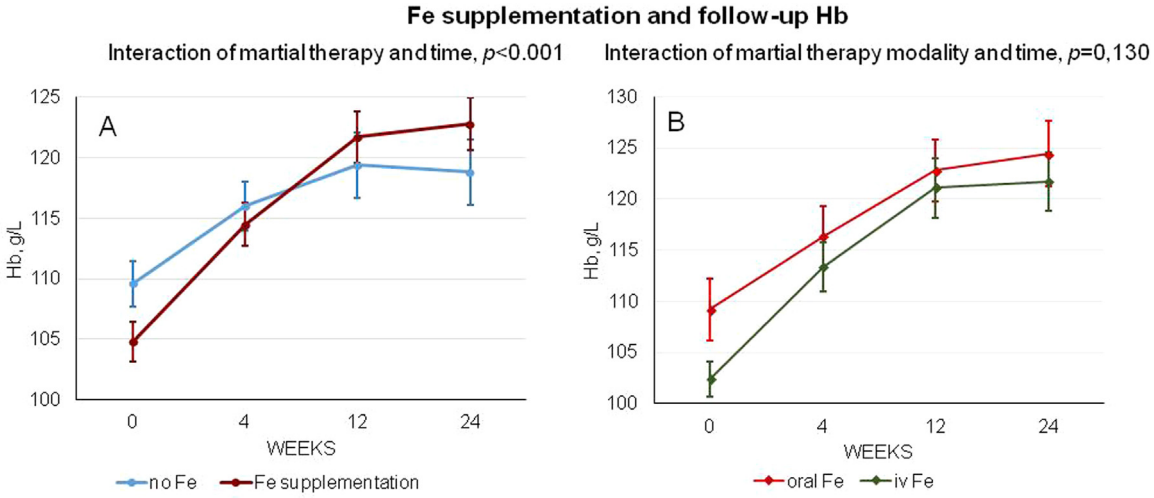

Fig. 4. Follow-up hemoglobin as influenced by iron supplementation. Hemoglobin concentrations are reported as means and 95% CI. Fe, iron; iv, intravenous..

disease at any time point during the study (Table 1). The low treatment rate of iron and vitamin deficiencies and persistence of some degree of inflammation throughout the study likely contributed to the high prevalence of anemia during follow-up, also in cases with quiescent disease. Both Hb and disease activity influenced fatigue and QoL; when separate analyses were conducted for patients with quiescent and those with active disease, Hb correlations with IBDQ were partially preserved in quiescent disease, but lost statistical significance in active disease. Hb correlations with fatigue, on the contrary, remained significant in both quiescent and active disease, indicating that these correlations are not exclusively due to the influence of disease activity on both fatigue and Hb and confirming the multifactorial pathogenesis of fatigue in IBD [30,31]. The relevance of fatigue in IBD has been recently emphasized by including investigation on the causes of fatigue among the top 10 research priorities in children and young adults with IBD [32].

Treatment of iron deficiency in IBD is a clinical priority [9]. Intravenous iron supplementation is usually considered as first-line treatment, whereas oral iron is reserved to patients with mild anemia and clinically quiescent disease. Oral iron has been suggested to produce mucosal harm and disease exacerbation in IBD, together with increased fecal calprotectin [33–36], possibly resulting in further reduction of iron absorption. In our study, oral iron supplementation was associated with Hb improvement over no treatment, without increasing the prevalence of active disease during follow-up. This apparently rules out a contribution of oral iron to development of active disease or disease exacerbations and confirms that oral iron represents an effective and safe treatment option for cases of mild anemia due to iron deficiency in IBD. We need to point out, however, that patients in the oral iron group probably had milder disease than those treated with parenteral iron; in addition, tolerability and side effects of different oral iron formulations were not investigated in this study and most patients in the oral iron group were treated with sucrosomial iron that is generally well tolerated, with very few side effects, but whose effectiveness in this setting has yet to be clearly demonstrated [37].

The reported association between lower baseline Hb concentrations and treatment with systemic steroids is likely related to the more frequent use of steroids at disease presentation or in the treatment of disease flares, when rapid symptom improvement is desirable; compared with other treatments, in fact, a higher proportion of steroid treated patients had baseline active disease. Although we do not have complete data concerning timing and duration of each treatment, in most cases steroids were used for periods lasting from few weeks to months as disease remission induction therapy; this explains the greater change from active to inactive disease reported in this group of patients.

4. Conclusions

Our study has some limitations related to its setting and design. Study participation was restricted to outpatients attending centers dedicated to IBD diagnosis and treatment; the study, therefore, may not accurately reflect the real world situation in primary care centers or in other settings. Treatments were not randomly assigned; reported effects of iron supplementation on Hb are therefore prone to selection bias, whereas confounding factors may have contributed to the described associations between anemia severity and fatigue or QoL. However, data concerning the long-term persistence of anemia and iron deficiency (up to 24 weeks), the high relapse rate of anemia and the association of anemia severity with active disease, increased C-reactive protein, reduced kidney function and higher prevalence of clinical complications/hospitalizations during follow-up are firmly established and confirm the contribution of anemia to disease burden in patients with IBD.

Author contributions

G. Bergamaschi, C.K., and A.D.S. participated in the study design, data analysis and interpretation, and writing the manuscript. All the authors participated in the collection of patient data, critically reviewed the manuscript, and read and approved the final manuscript. G.Bergamaschi and A.D.S. are the article guarantors.

Funding

No specific funding. This work was supported by the Italian Group for Inflammatory Bowel Diseases (IG-IBD); the Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia; and the University of Pavia, Pavia, Italy.

Data Availability Statement

The data underlying this article will be shared on reasonable request to the corresponding author.

Conflict of interest

The Authors have no conflict of interest to declare. No specific funding. This work was supported by the Italian Group for Inflammatory Bowel Diseases (IG-IBD); the Istituto di Ricovero e Cura a Carattere Scientifico Policlinico San Matteo, Pavia; and the University of Pavia, Pavia, Italy. No specific funding was obtained.

Acknowledgments

The RIDART I investigators are Giuseppe Amodeo[10], Elisabetta Antonelli[19], Noemi Bertetti[14], Cristina Bezzio[9], Michele Campigotto[24], Roberta Caccaro[3], Manuela De Bona[21], Cristina Della Corte[9], Maria G. Demarzo[5,17], Giuliano Falasco[16], Rosanna Fontana[12], Paolo Gionchetti[8], Paola Iovino[7], Federica Lepore[1], Greta Lorenzon[3], Veronica Marasco[7], Alessandro Paolini[24], Lucienne Pellegrini[2], Alberto Pieraccini[30], Tiziana Pinto-Vraca[5], Davide Ribaldone[4], Giulia Rizzuto[11], Jenny Roselli[6], Giovanni Santacroce[1], Alessia Todeschini[13], Marta Vernero[4], Anna Viola[5], Irene Zammarchi[15].

1. Medicina Generale I, Fondazione IRCCS Policlinico San Matteo e Università di Pavia, 27100 Pavia, Italy.
2. Gastroenterology, Department of Clinical Medicine and Surgery, University Federico II of Naples, 80138 Naples, Italy.
3. Inflammatory Bowel disease Unit- AO-University of Padua, 35122 Padova, Italy.
4. Gastroenterology and Digestive Endoscopy Unit, "Città della Salute e della Scienza" Hospital, 10126 Torino, Italy.
5. Gastroenterology and Clinical Unit for inflammatory bowel diseases, Dept. of Clinical and Experimental Medicine; University of Messina, 98122 Messina, Italy.
6. Unità operativa complessa di Gastroenterologia clinica, Azienda ospedaliero universitaria Careggi- Firenze, 50134 Firenze, Italy.
7. Gastroenterology and Endoscopy Unit, AOU San Giovanni di Dio e Ruggi d'Aragona and University of Salerno, 84084 Salerno, Italy.
8. Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.
9. Gastroenterology Unit, Rho Hospital, ASST Rhodense, 20017 Rho (MI), Italy.
10. Gastroenterology Unit, Department of Medicine, A.O.U.I. Policlinico G.B. Rossi & University of Verona, 37134 Verona, Italy.
11. Inflammatory Bowel Disease Unit, A.O.O.R. "Villa Sofia-Cervello", 90146 Palermo Italy.

12. Department of Gastroenterology and Endoscopy, Fondazione "Casa Sollievo della Sofferenza", IRCCS, 71013 San Giovanni Rotondo, Italy.
13. Gastroenterology Unit (D.E.T.O.), University of Bari, 70121 Bari, Italy.
14. Division of Gastroenterology, Department of Translational and Precision Medicine, "Sapienza" University of Rome and Umberto I Hospital, 00161 Rome, Italy.
15. Dept of Experimental and Clinical Science, University of Brescia, Gastroenterology Unit, Spedali Civili Hospital, 25123 Brescia, Italy.
16. Gastroenterology and Endoscopy Unit, Azienda Ospedaliera San Camillo-Forlanini, 00152 Rome, Italy, and Villa Stuart, Multi-Speciality Clinic, 00135 Rome, Italy.
17. Gastroenterology unit, Department of Internal medicine, Policlinico San Martino, Università di Genova, 16132 Genoa, Italy.
19. Gastroenterology, Hepatology & Digestive Endoscopy Section, Department of Medicine & Surgery, University of Perugia and Perugia General Hospital, 06129 Perugia, Italy.
21. Department of Gastrointestinal Oncological Surgery, Gastroenterology Unit, S. Maria del Prato Hospital, 30032 Feltre , Italy.
24. Gastroenterology and Digestive Endoscopy Unit, Cattinara Academic Hospital, 34149 Trieste, Italy.
30. UO Gastroenterologia ed Endoscopia Digestiva, Ospedale San Jacopo, 51100 Pistoia, Italy.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2024.01.176.

References

[1] Bergamaschi G, Di Sabatino A, Corazza GR. Pathogenesis, diagnosis and treatment of anaemia in immune-mediated gastrointestinal disorders. Br J Haematol 2018;182(3):319–29.
[2] Cucino C, Sonnenberg A. Cause of death in patients with inflammatory bowel disease. Inflamm Bowel Dis 2001;7(3):250–5. doi:10.1097/00054725-200108000-00011.
[3] Pizzi LT, Weston CM, Goldfarb NI, et al. Impact of chronic conditions on quality of life in patients with inflammatory bowel disease. Inflamm Bowel Dis 2006;12(1):47–52.
[4] Wells CW, Lewis S, Barton JR, et al. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflamm Bowel Dis 2006;12(2):123–30.
[5] Filmann 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(5):936–45.
[6] Patel D, Yang YX, Trivedi C, et al. Incidence, duration, and management of anemia: a nationwide comparison between IBD and non-IBD populations. Inflamm Bowel Dis 2020;26(6):934–40.
[7] Gasche C, Berstad A, Befrits R, et al. Guidelines on the diagnosis and management of iron deficiency and anemia in inflammatory bowel diseases. Inflamm Bowel Dis 2007;13(12):1545–53.
[8] Dignass AU, Gasche C, Bettenworth D, et al. European consensus on the diagnosis and management of iron deficiency and anaemia in inflammatory bowel diseases. J Crohns Colitis 2015;9(3):211–22.
[9] Patel D, Trivedi C, Khan N. Management of anemia in patients with inflammatory bowel disease (IBD). Curr Treat Options Gastroenterol 2018;16(1):112–28.
[10] Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68(Suppl 3):s1–s106.
[11] Goyal A, Zheng Y, Albenberg LG, et al. Anemia in children with inflammatory bowel disease: a position paper by the IBD Committee of the North American Society of Pediatric Gastroenterology, Hepatology and Nutrition. J Pediatr Gastroenterol Nutr 2020;71(4):563–82.
[12] Coe CL, Meyers MH, Beaulieu DB, et al. Gastroenterologist-lead management of iron deficiency anemia in inflammatory bowel disease is effective, safe, and may increase quality of life. Crohns Colitis 360 2020;2(3):otaa051.
[13] Kulnigg S, Teischinger L, Dejaco C, et al. Rapid recurrence of IBD-associated anemia and iron deficiency after intravenous iron sucrose and erythropoietin treatment. Am J Gastroenterol 2009;104(6):1460–7.
[14] Evstatiev R, Alexeeva O, Bokemeyer B, et al. FERGI Study Group: ferric carboxymaltose prevents recurrence of anemia in patients with inflammatory bowel disease. Clin Gastroenterol Hepatol 2013;11(3):269–77.
[15] Bergamaschi G, Castiglione F, D'Incà R, et al. Prevalence, pathogenesis and management of anemia in inflammatory bowel disease: an IG-IBD multicenter, prospective, and observational study. Inflamm Bowel Dis 2022;29(1):76–84.
[16] Ott C, Liebold A, Takses A, et al. High prevalence but insufficient treatment of iron-deficiency anemia in patients with inflammatory bowel disease: results of a population-based cohort. Gastroenterol Res Pract 2012;2012:595970.
[17] Miller SD, Cuffari C, Akhuemonkhan E, et al. Anemia screening, prevalence, and treatment in pediatric inflammatory bowel disease in the United States, 2010-2014. Pediatr Gastroenterol Hepatol Nutr 2019;22(2):152–61.
[18] Best WR, Becktel JM, Singleton JW, et al. Development of a Crohn's disease activity index: National Cooperative Crohn's Disease Study. Gastroenterology 1976;70(3):439–44.
[19] Rachmilewitz D. Coated mesalazine (5-aminosalicylic acid) versus sulphasalazine in the treatment of active ulcerative colitis: a randomised trial. BMJ 1989;298(6666):82–6.
[20] Ciccocioppo R, Klersy C, Russo ML, et al. Validation of the Italian translation of the Inflammatory Bowel Disease Questionnaire. Dig Liver Dis 2011;43(7):535–41.
[21] Guyatt G, Mitchell A, Irvine EJ, et al. A new measure of health status for clinical trials in inflammatory bowel disease. Gastroenterology 1989;96:804–10.
[22] Satsangi J, Silverberg MS, Vermeire S, et al. The Montreal classification of inflammatory bowel disease: controversies, consensus, and implications. Gut 2006;55:749–53.
[23] WHO/UNICEF/UNU Iron deficiency anaemia assessment, prevention, and control: a guide for programme managers. Geneva: World Health Organization; 2001 http://www.who.int/nutrition/publications/en/ida_assessment_prevention_control.pdf Accessed December 2012.
[24] Weiss G, Ganz T, Goodnough LT. Anemia of inflammation. Blood 2019;133(1):40–50.
[25] Weiss G, Goodnough LT. Anemia of chronic disease. N Engl J Med 2005;352(10):1011–23.
[26] Inker LA, Eneanya ND, Coresh J, et al. Chronic kidney disease epidemiology collaboration. New creatinine- and Cystatin C-based equations to estimate GFR without race. N Engl J Med 2021;385(19):1737–49.
[27] GBD 2021 Anaemia CollaboratorsPrevalence, years lived with disability, and trends in anaemia burden by severity and cause, 1990-2021: findings from the Global Burden of Disease Study 2021. Lancet Haematol 2023;10(9):e713–ee34.
[28] Bergamaschi G, Di Sabatino A, Albertini R, et al. Prevalence and pathogenesis of anemia in inflammatory bowel disease. Influence of anti-tumor necrosis factor-alpha treatment. Haematologica 2010;95(2):199–205.
[29] Graff LA, Clara I, Walker JR, et al. Changes in fatigue over 2 years are associated with activity of inflammatory bowel disease and psychological factors. Clin Gastroenterol Hepatol 2013;11(9):1140–6.
[30] Bager P, Befrits R, Wikman O, et al. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. Aliment Pharmacol Ther 2012;35(1):133–41.
[31] McGing JJ, Radford SJ, Francis ST, et al. Review article: the aetiology of fatigue in inflammatory bowel disease and potential therapeutic management strategies. Aliment Pharmacol Ther 2021;54(4):368–87.
[32] Jagt JZ, van Rheenen PF, Thoma SMA, et al. Kids with Crohn's and Colitis (KiCC) Working Group for Collaborative Paediatric IBD Research in the Netherlands. The top 10 research priorities for inflammatory bowel disease in children and young adults: results of a James Lind Alliance Priority Setting Partnership. Lancet Gastroenterol Hepatol 2023;8(8):690–1.
[33] De Silva AD, Tsironi E, Feakins RM, et al. Efficacy and tolerability of oral iron therapy in inflammatory bowel disease: a prospective, comparative trial. Aliment Pharmacol Ther 2005;22:1097–105.
[34] Seril DN, Liao J, West AB, et al. High-iron diet: foe or feat in ulcerative colitis and ulcerative colitis-associated carcinogenesis. J Clin Gastroenterol 2006;40:391–7.
[35] Zimmermann MB, Chassard C, Rohner F, et al. The effects of iron fortification on the gut microbiota in African children: a randomized controlled trial in Cote d'Ivoire. Am J Clin Nutr 2010;92:1406–15.
[36] Aksan A, Wohlrath M, Iqbal TH, et al. Inflammation, but not the underlying disease or its location, predicts oral iron absorption capacity in patients with inflammatory bowel disease. J Crohns Colitis 2020;14(3):316–22.
[37] Gómez-Ramírez S, Brilli E, Tarantino G, et al. Sucrosomial® iron: an updated review of its clinical efficacy for the treatment of iron deficiency. Pharmaceuticals 2023;16(6):847 2023.