



## 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)



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## 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.

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## 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<sub>12</sub> 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.

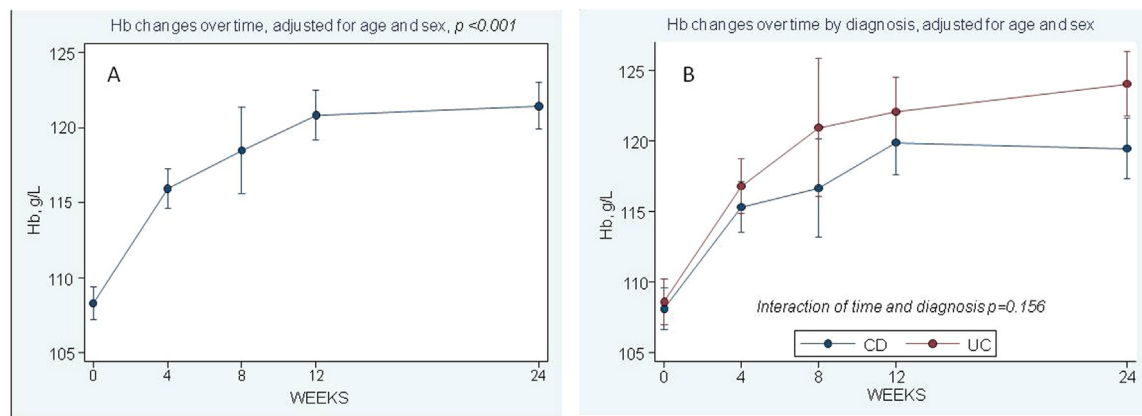
## 2. Patients and methods

## 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].<sup>15</sup>

## 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 hemoglobin 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 (Infl-IDA) was characterized by transferrin saturation < 20% and serum ferritin  $\geq 30$  but  $\leq 100$   $\mu\text{g/L}$  [24,25]. Cut-off values for the diagnosis of vitamin deficiencies were serum vitamin B12 < 200 ng/L and folate < 2.0  $\mu\text{g/L}$ . 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  $\geq 10$  g/L or  $\geq 20$  g/L compared with baseline were determined during the follow-up of RIDART I patients (Hb normalization or an elevation  $\geq 10$  g/L or  $\geq 20$  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.

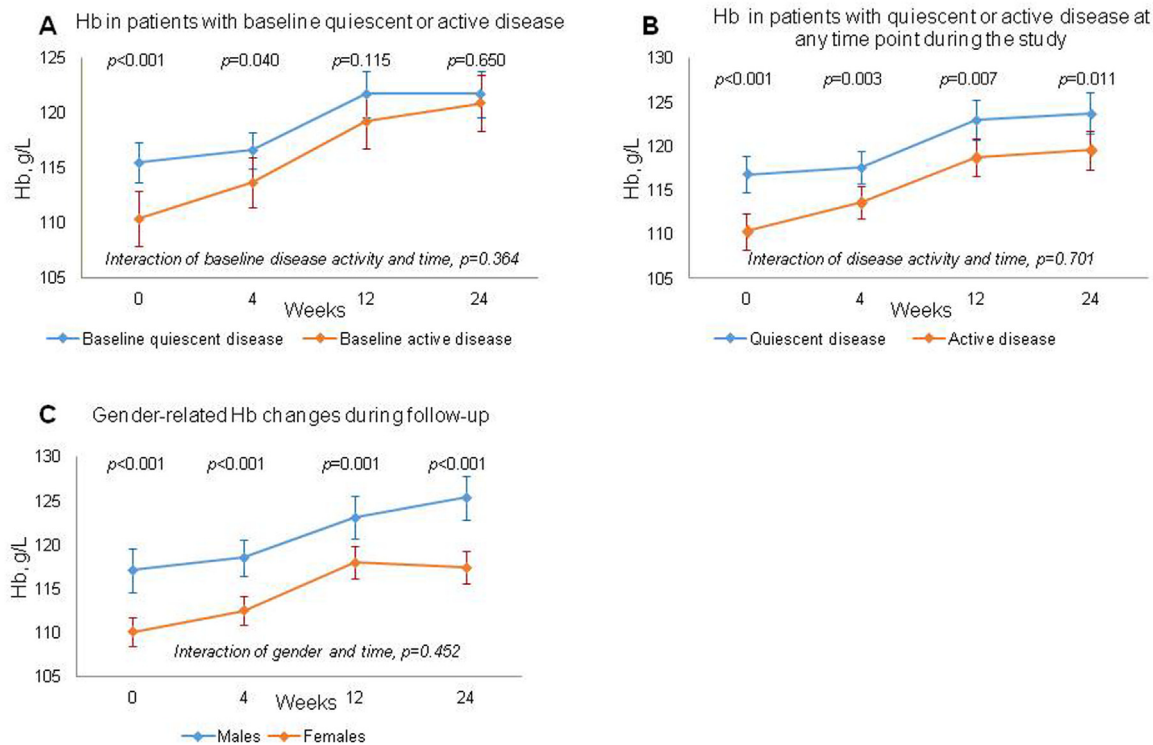
Hb improved over time in both CD and UC (Fig. 1B); at week 24, however, improvement was greater in UC ( $p = 0.037$ ). Similarly, more UC than CD patients achieved Hb normalization or a Hb increase  $\geq 10$  or 20 g/L within week 24 (supplementary Table 2). Considering the whole patient population, 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  $\geq 10$  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 InflIDA, but Hb elevation during follow-up was greater in IDA compared with InflIDA 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       | —                 | 182 (47) 390    | 211 (60) 349    | 204 (61) 335    | < 0.001 |
| Hb increase, N (%)                 | —                 | 130 (33) 390    | 171 (49) 349    | 165 (49) 335    | < 0.001 |
| Hb normalization or ≥ 20 g/L       | —                 | —               | —               | —               | < 0.001 |
| Hb increase, N (%)                 | —                 | —               | —               | —               | < 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 <sup>2</sup>   | 106 (92–118)*     | —               | —               | —               | —       |

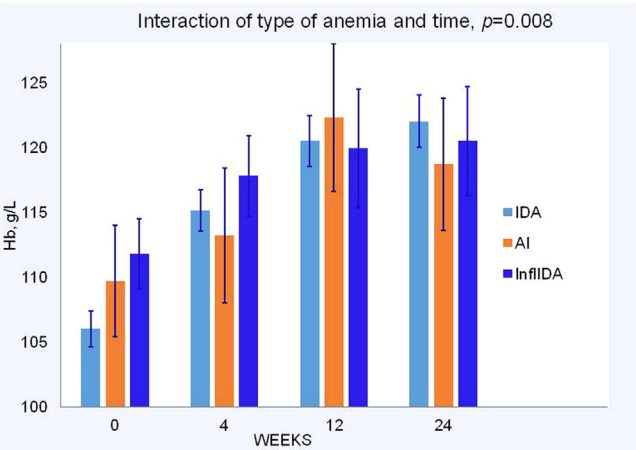
FU, follow-up; Hb, hemoglobin; CD, Crohn's disease; UC, ulcerative colitis; N, number of patients; IBDQ, Inflammatory Bowel Disease Questionnaire; CRP, C-reactive protein; NS, not significant. Values are reported as medians and interquartile ranges or numbers of patients and%. Continuous variables with 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; InflIDA, anemia of inflammation associated with iron deficiency.

course of the study (supplementary Table 5). Vitamin B<sub>12</sub> 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).

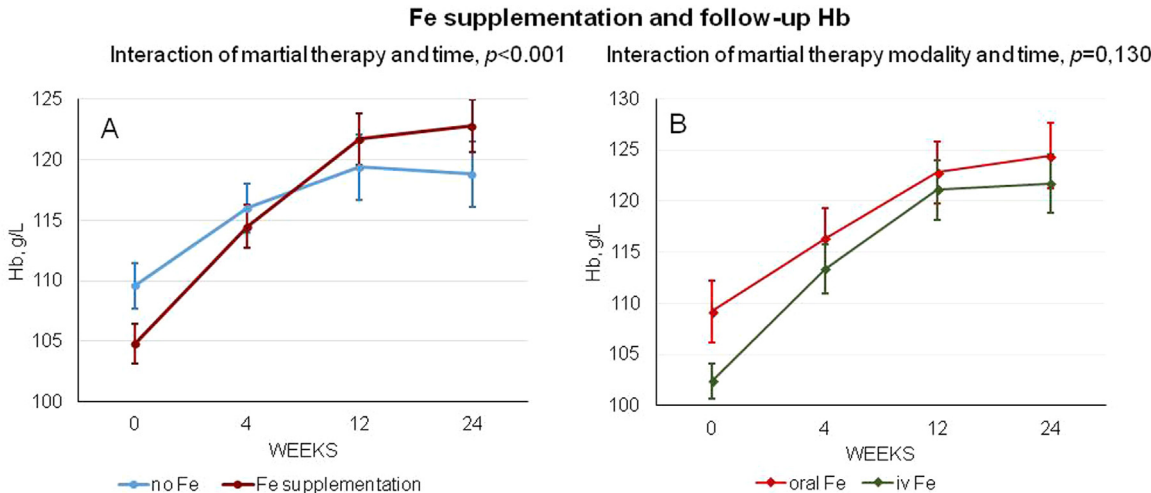
Quiescent disease and higher Hb concentrations were associated with less fatigue and better QoL at any time point during the study (supplementary Tables 8 and 9). Fatigue improved during follow-up (Table 1); improvement was not influenced by iron treatment (supplementary Figure 2A), but was greater in 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.

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#### Data Availability Statement

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

#### Conflict of interest

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## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.dld.2024.01.176](https://doi.org/10.1016/j.dld.2024.01.176).

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