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Prevalence of Anemia and Iron Deficiency in Romanian Patients with Inflammatory Bowel Disease: a Prospective Multicenter Study

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ABSTRACT

Background & Aims: Anemia is the most frequent systemic complication in inflammatory bowel diseases. It affects the quality of life and can interact with working capacity. Our objectives were to identify the prevalence of anemia, its main causes and its management in patients with inflammatory bowel disease from Romania.
Methods: We conducted a multicenter prospective study from March 2013 to August 2014. We enrolled 291 patients from three referral centers: 115 (39.52%) with Crohn's disease (CD) and 176 (60.48%) with ulcerative colitis (UC). We defined anemia according to the WHO criteria.
Results: Median age of the patients was 41 years and the median time period since diagnosis was 3 years (0.75-7). The median activity index for UC (UCAI) was 4 and the median CD activity index (CDAI) was 96. More patients with CD were on antiTNFα therapy ($p < 0.01$), corticosteroids ($p = 0.18$) or azathioprine ($p = 0.05$) and required surgery for their underlying disease at study enrollment ($p < 0.01$). Anemia was present in 31.27% of the patients, more often in those with CD (35.65%) than with UC (28.41%) (not statistically significant); 53.26% of the patients had iron deficiency while 4.12% had folic acid and 8.59% vitamin B12 deficiency; 9.62% of the patients had received anti-anemic therapy at inclusion in the study or in the last three months prior to study enrollment.
Conclusions: About one in three Romanian patients with inflammatory bowel disease has anemia, which is frequently associated with iron deficiency. About 30% of the patients with anemia are under therapy and the most frequent route for iron supplementation is the oral one. This might contribute to the high prevalence of iron deficiency and the low level of compliance.

Key words: anemia – iron deficiency – inflammatory bowel disease.

Abbreviations: ACD: anemia of chronic disease; CD: Crohn's disease; CDAI: Crohn's disease activity index; CRP: C-reactive protein; ESA: erythropoiesis stimulating agents; Hb: hemoglobin; IBD: inflammatory bowel disease; IDA: iron deficiency anemia; TfS: transferrin saturation; TNFα: tumor necrosis factor alpha; UC: ulcerative colitis; UCAI: ulcerative colitis (Mayo) activity index.

INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic idiopathic diseases that present with periods of relapses and remissions in their clinical course. Inflammatory bowel diseases affect only the colonic mucosa, in ulcerative colitis (UC), or can be characterized by transmural inflammation and affect any part of the gastrointestinal tract, as in Crohn's disease (CD).

Anemia is the most frequent complication of IBD [1]. In the presence of this complication, patients with IBD might have a poor quality of life, a decreased feeling of wellbeing, cognitive function and physical performance. Anemia is a condition that can increase the duration of hospitalization in hospitalized patients and also IBD mortality. According to the definition of the WHO, the cutoff point for anemia is a hemoglobin (Hb) level below 12g/dL for non-pregnant females and below 13g/dL for males [2]. In patients with IBD, the main causes of anemia are iron deficiency and chronic inflammation. There are also other causes of anemia such as hemolytic anemia, drug-induced anemia (sulfasalazin, thiopurines, methotrexate), and vitamin B12 and folic acid deficiency.

MATERIAL AND METHODS

The purpose of our study was to evaluate the prevalence of anemia and iron deficiency in an unselected group of patients with IBD and the secondary objectives were to identify the causes of anemia and its management in a population with IBD from Romania.

For the purpose of this study we enrolled prospectively between March 2013 and August 2014 patients with IBD from three University Hospitals in Bucharest, Timisoara and Cluj. The diagnosis of CD or UC was confirmed by the clinical, endoscopic, radiologic and histopathological criteria generally accepted [3]. Patients were excluded if they were younger than 18 years, if they had a prior gastrectomy or a history of malignancy. Pregnant women or nursing mothers were also not included. All enrolled patients read and signed an informed consent that was approved by the Ethics Committee of the universities.

The classification and extension of the disease in patients with IBD were assessed using the Montreal classification. Crohn's disease activity was measured according to CD activity index (CDAI). For UC we used the Mayo activity index (UCAI).

The anemia workup included complete blood count, serum iron and ferritin levels, transferrin saturation (TfS), serum levels of vitamin B12 and folic acid, C-reactive protein (CRP).

Iron deficiency anemia (IDA) was diagnosed by anemia associated with low serum iron, low serum ferritin and low TfS. In the absence of clinical or biochemical (i.e. CRP < 5mg/L) data suggestive of disease activity we considered as iron deficiency a serum ferritin below 30μg/L or TfS < 20%. In the presence of chronic inflammation (CRP > 5mg/L), IDA was diagnosed as a ferritin level < 100μg/L and/or a TfS < 20%. In active IBD, the proinflammatory cytokines and hepcidin can alter iron metabolism by blocking the iron in the endoplasmic reticulum, by interfering with erythropoiesis and apoptosis. This condition, called anemia of chronic disease (ACD) [4] was diagnosed by a ferritin level > 100ug/L and a TfS <20% in the presence of inflammation. Ferritin level between 30 and 100ug/L is diagnostic for the combination of IDA and ACD, a condition termed mixed anemia.

Data collection and statistical analysis

To test the differences between groups for qualitative data, chi square test and Fisher exact test were used. Differences between the two independent groups of quantitative data were tested with the Wilcoxon rank sum test for non normally distributed data. Differences between more than two independent groups of quantitative data were tested with the Kruskal Wallis test for non normally distributed data, followed by Tukey Kramer post hoc tests for pairwise comparisons. Data was assessed for normality using quantile-quantile plots, strip charts, histograms and Saphiro-Wilk test. For all tests the two tail p value was used [5].

RESULTS

We found that among IBD patients, more had CD in the south (Bucharest) and eastern (Timisoara) region of the country, as opposed to UC that was more often diagnosed in the western region (Cluj) (Table I). The severity scores showed that the majority of our population with IBD was in remission or with a mild flair of activity at study enrollment (i.e. CDAI <150). We noted a tendency for increased use of immunosupressors and anti TNFα in patients with CD as opposed to patients with UC that received more often 5-aminosalicylic acid therapy (Table II). After a median time of 3 years from the diagnosis, more than 10% of the patients with CD underwent at least one surgical intervention for fistulae or strictures (Table II).

Table I. Characteristics of the studied patients with inflammatory bowel disease

	All patients n (%)	Gastroenterology department			
		Bucharest	Cluj	Timisoara	p-value
IBD	291	101 (34.71)	85 (29.21)	105 (36.08)	
CD (%)	115 (39.52)	55 (54.46)	19 (22.35)	41 (39.05)	<0.01
UC (%)	176 (60.48)	46 (45.54)	66 (77.65)	64 (60.95)	<0.01
Sex (F)	124 (42.61)	39 (38.61)	37 (43.53)	48 (45.71)	0.58
Years with IBD mean (range)	3 [0.75-6]	4 [2-7]	2 [1-4]	3 [0.75-6]	<0.01
Age (yrs) mean (range)	41 [28-55]	39 [28-55]	41 [32-51]	43 [31-55]	0.7

IBD: inflammatory bowel disease; CD: Crohn's disease; UC: ulcerative colitis

Although the median Hb level in our group of patients was normal (i.e. 13.3g/dl), the median values for ferritin and TfS indicate a trend towards iron deficiency in the study population, which highlights the importance of a complete periodic anemia workup in patients with IBD (Table III) [6].

The overall prevalence of anemia was 31.3%, similar among patients with CD and UC; 53.3% of the population with IBD had iron deficiency. Anemia of chronic disease, anemia due to vitamin B12 and folic acid deficiency, and mixed anemia were rare (Tables III, IV).

Less than 10% of the studied patients and about 30% of the anemic patients received treatment. The most common route of iron supplementation was oral, followed by intravenous iron and blood transfusions. Twenty patients (7%) received blood transfusions to correct anemia before/at study enrollment (Table V). We did not follow up these patients.

DISCUSSION

The presence of anemia affects patients' quality of life and interferes with their working capacity. Our study demonstrates the magnitude of anemia prevalence in a population with IBD from Romania. To our knowledge, this is the first multicenter study that shows the most important causes of anemia and the therapeutic strategies used to control this complication in our country.

The prevalence of anemia in our patients was 31%. This prevalence is slightly higher than that published recently in a

Table II. Inflammatory bowel disease phenotype, severity and type of treatment in our patiens

IBD patients	Crohn's disease	Ulcerative colitis	P-value
n (%)	115 (39.52)	176 (60.48)	
Sex Female, n (%)	49 (42.61)	75 (42.61)	0.9
Years with IBD, median [IQR]	3 [1 - 6]	3 [1 - 6]	0.5
Vienna classification for CD			
Age at diagnosis n (%)	A1: 36 (31.3)		
	A2: 64 (55.65)		
	A3: 15 (13.04)	-	
Behavior CD, n (%)	B1: 76 (66.09)		
	B2: 24 (20.87)		
	B3: 15 (13.04)	-	
CD localization, n (%)	L1: 21 (18.26)		
	L2: 56 (48.7)		
	L3: 37 (32.17)	-	
	L4: 1 (0.87)		
Montreal classification for UC, n (%)	-	E0: 1 (0.57)	
		E1: 42 (24)	
		E2: 79 (45.14)	
		E3: 52 (29.71)	
		No data: 2 (1.14)	
Severity			
UCAI, median [IQR]	-	4.00 [2.00, 5.00]	
CDAI, median [IQR]	96 [51, 145]	-	
Treatment			
Azathioprine, n (%)	38 (34.86)	41 (24.12)	0.05
Surgery, n (%)	9 (10.84)	3 (1.76)	<0.01
Corticosteroid, n (%)	33 (30.84)	40 (23.53)	0.18
Anti TNFα, n (%)	60 (52.63)	24 (14.04)	<0.01
Other immunosuppressive therapy, n (%)	2 (1.87)	2 (1.18)	0.64
5-aminosalicylic acid, n (%)	47 (42.73)	155 (90.12)	<0.01

CD: Crohn's disease; UC: ulcerative disease; UCAI: ulcerative colitis (Mayo) activity index; CDAI: Crohn's disease activity index

meta-analysis by Filmann et al: 24% of 2,192 European patients with IBD had anemia [7]. Other studies show that up to 68% of inpatients with IBD had anemia [8, 9]. The differences between the prevalence of anemia in IBD depend strongly on the studied population; for example, in the study of Bager et al, the study population consisted only of outpatients with IBD and anemia prevalence was found to be 19% [10]. Anemia reappears in more than 50% of patients with IBD after one year [11] and this complication is traditionally considered to be directly correlated with the active flairs of the underlying disease. Sometimes, IBD is diagnosed only when the first symptoms of anemia occur.

In our study, there was a higher prevalence of the inflammatory syndrome (i.e. CRP > 5 mg/L) in patients with CD as opposed to patients with UC ($p < 0.01$) (Table III). This data is in accordance with a study which demonstrates an association between active IBD, especially CD, and high CRP levels in 40-80% of patients [12]. However, this data does not translate into a significantly higher prevalence of anemia in CD as opposed to UC (p=0.19) (Table III).

In the group of patients with anemia, 78% had iron deficiency and 8.8% had ACD. In individuals with IBD these two conditions commonly overlap. It is well known that blood loss in the bowel, systemic iron sequestration and reduced iron absorption secondary to gut inflammation lead to a negative iron balance in IBD. Also the release of interleukin 6 increases the hepatic synthesis of hepcidin which leads to the retention of iron in the reticulo-endothelial system and potentially to a reduced duodenal absorbtion. Our results show that in 15.4% of the patients with anemia, IDA and ACD overlap.

Anemia therapy should be taken into consideration for every patient with a hemoglobin level below normal [13, 14] and iron substitution is recommended for every anemic patient who has iron deficiency [15-17]. It is known that treating only the underlying disease is not enough to corect the Hb levels [18].

Normally, about 10% of the oral iron is absorbed from the gut and the unabsorbed iron can lead to bloating, abdominal pain, nausea or diarrhea. In the presence of chronic bowel inflammation, activated T lymphocytes diminish even more

Table III. Prevalence of anemia and iron deficiency in our patients with inflammatory bowel disease

	All patients	Crohn's disease	Ulcerative colitis	P-value CD/UC
	291 (100)	115 (39.52)	176 (60.48)	
Sex (Female/Male), n (%)	124 (42.61) / 167 (57.39)	49 (42.61) / 66 (57.39)	75 (42.61) / 101 (57.39)	0.9
Hemoglobin (g/dL), median [IQR]	13.3 [11.8 – 14.5]	13.3 [11.7 - 14.3]	13.55 [12 - 14.8]	0.13
Ferritin (ng/mL), median [IQR]	68.6 [25.40 – 149.05]	76.2 [25.35 - 156]	59.19 [26.45 - 142.62]	0.67
Anemia, n (%)	91 (31.27)	41 (35.65)	50 (28.41)	0.19
Inflammation (CRP > 5 mg/L), n (%)	56 (19.24)	31 (26.96)	25 (14.2)	<0.01
Transferrin saturation, median [IQR]	18 [12 – 25.85]	17.59 [10 - 23.19]	19 [13 - 26.58]	0.1
Iron deficiency anemia, n (%)	71 (24.4)	29 (25.22)	42 (23.86)	0.79
Anemia with folic acid deficiency, n (%)	5 (1.72)	3 (2.61)	2 (1.14)	0.39
Anemia with vitamin B12 deficiency, n (%)	8 (2.75)	6 (5.22)	2 (1.14)	0.06
Iron deficiency anemia (IDA), n (%)	155 (53.26)	60 (52.17)	95 (53.98)	0.76
Iron deficiency without anemia, n (%)	36 (12.37)	15 (13.04)	21 (11.93)	0.78
Anemia of chronic disease (ACD), (%)	8 (2.75)	4 (3.48)	4 (2.27)	0.72
Mixed anemia (IDA+ACD) n (%)	14 (4.81)	9 (7.83)	5 (2.84)	0.11
Folic acid deficiency (< 4.6 ng/ml), n (%)	12 (4.12)	6 (5.22)	6 (3.41)	0.55
Vitamin B12 deficiency (< 191 pg/ml), n (%)	25 (8.59)	15 (13.04)	10 (5.68)	0.03

Table IV. Causes of anemia in IBD patients

	Patients with anemia	CD	UC	p value CD/UC
	91 (100)	41 (45.05)	50 (54.95)	
Inflammation, n (%)	35 (38.46)	20 (48.78)	15 (30)	0.07
Iron deficiency, n (%)	71 (78.02)	29 (70.73)	42 (84)	0.13
Mixed anemia, n (%)	14 (15.38)	9 (21.95)	5 (10)	0.15
ACD, n (%)	8 (8.79)	4 (9.76)	4 (8)	1
Folic acid deficiency, n (%)	5 (5.49)	3 (7.32)	2 (4)	0.65
Vitamin B12 deficiency, n (%)	8 (8.79)	6 (14.63)	2 (4)	0.13

CD: Crohn's disease; UC: ulcerative colitis; ACD: anemia of chronic disease

oral iron absorption. Furthermore, less than half of the patients with IBD that receive oral iron supplementation tolerate the entire dose that is necessary to restore their iron deposits and normalize hemoglobin levels [19, 20]. Intravenous iron substitution is recommended for patients that require rapid hemoglobin correction, for cases of severe anemia and for those that are taking erythropoiesis stimulating agents (ESA). Blood transfusions may increase the risk for arterial and venous thromboembolic events [21], a risk that is already higher than in the general population because of the chronic inflammatory process and the activated cytokines. Transfusions can also lead to immunomodulation and infections [22-24]. All these possible adverse events make blood transfusions the last resort, namely for severe anemia and for the acute forms with hemodynamic instability.

In our population with IBD, only 6.9% of the patients followed some therapy of anemia at enrollment in the study. However, we did not perform a follow-up after study enrollment to identify anemia management changes after complete anemia workup results, which will be adressed in a future longitudinal study. We observed that the primary form of iron substitution in our patients was oral substitution (25.9%), followed by intravenous iron (17.9%) and blood transfusions (7.14%); ESA (1.1%) were rarelly used to correct hemoglobin levels and iron deficiency. These results are somewhat inconsistent with the

Table V. Type of therapy in the patients with inflammatory bowel disease and anemia

	All patients n (%)	CD	UC	P-value CD/UC
	291 (100)	115 (39.52)	176 (60.48)	
Currently or in the last 3 months on antianemic therapy	28 (9.62)	14 (12.17)	14 (7.95)	0.23
Currently on antianemic treatment	20 (6.87)	10 (8.7)	10 (5.68)	0.32
ESA in the past	3 (1.09)	2 (1.89)	1 (0.59)	0.56
I.V. iron in the past	50 (17.86)	25 (23.15)	25 (14.53)	0.07
Oral iron in the past	72 (25.9)	37 (34.58)	35 (20.47)	<0.01
Blood transfusions in the past	20 (7.14)	7 (6.48)	13 (7.56)	0.73

ESA: erythropoiesis stimulating agents; CD: Crohn's disease; UC: ulcerative colitis;

European guidelines recommendations and the data in the medical literature [16].

One of the limitations of this study is the fact that we have not assessed the relationships among disease activity, CRP level and anemia. Another limitation is the fact that the studied group of patients with IBD was evaluated only in university departments of gastroenterology and the prevalence of anemia might not correctly reflect the true burden of anemia in the general population with IBD. Thus, our data should be interpreted in the appropriate context. Finally, we appreciate that future research in longitudinal studies is required to examine the impact of more aggressive and rapid management of IBD and IBD complications.

CONCLUSIONS

One in three patients with IBD that addressed our medical centers had anemia and the primary cause of it was iron deficiency. The management of these patients has been insufficient, based often on oral iron supplements and blood transfusions, a good reason to decide it is time to improve follow-up and treatment of this complication in our patients with IBD.

Conflicts of interest: All authors disclose no conflicts of interest.

Authors contribution: A.L.: data aquisition, analysis and interpretation of data, drafting of the manuscript, study design and supervision. M.D.: study concept and design, obtained funding, supervised the study and revised the manuscript for important intellectual content. R.D., I.V., C.L., R.C., R.V.: data aquisition. M.T., A.T., C.G., L.G., A.G.: revised the manuscript for important intellectual content.

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REFERENCES

1. Gasche C, Lomer MC, Cavill I, Weiss G. Iron, anemia, and inflammatory bowel diseases. Gut 2004; 53: 1190-1197.doi: 10.1136/gut.2003.035758
2. World Health Organization, "Iron deficiency anemia assessment, prevention and control. A guide for programme managers," Report WHO/NHP/01.3, World Health Organization, Geneva, Switzerland, 2011.
3. van Assche G, Dignass A, Bokemeyer B, et al. Second European evidence-based consensus on the diagnosis and management of ulcerative colitis part 3: special situations. J Crohns Colitis 2013; 7: 1-33.doi: 10.1016/j.crohns.2012.09.005
4. Weiss G., Goodnough LT. Anemia of chronic disease. N Engl J Med 2005; 352: 1011–1023. doi: 10.1056/NEJMra041809
5. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing: Vienna, Austria; 2014. Available from: http://www.r-project.org/
6. Guagnozzi D, Severi C, Ialongo P, et al. Ferritin as a simple indicator of iron deficiency in anemic IBD patients. Inflamm Bowel Dis 2006; 12: 150–151.doi: 10.1097/01.MIB.0000199223.27595.e3
7. 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: 936-945. doi: 10.1097/01.MIB.0000442728.74340.fd
8. Alvarenga Antunes CV, Hallack Neto AA, Alvarenga Nascimento CR, et al. Anemia in inflammatory bowel disease outpatients: prevalence, risk factors, and etiology. BioMed Research International. Hindawi Publ Corp, article ID 728925, 12 Nov 2014.
9. Dumitrescu G, Dranga M, Pintilie IA, Nedelciuc O, Mihai C, Prelipcean CC. The prevalence of anaemia in patients with inflammatory bowel diseases in North-Eastern Romania. Rev Med Chir Soc Med Nat Iasi 2012; 116: 968-974.
10. Bager P, Befrits R, Wikman O, et al. The prevalence of anemia and iron deficiency in IBD outpatients in Scandinavia. Scand J Gastroenterol 2011; 46: 304-309.doi: 10.3109/00365521.2010.533382
11. Kulnigg S, Teischinger L, Dejaco C, Waldhor T, Gasche C. Rapid recurrence of IBD-associated anemia and iron deficiency after intravenous iron sucrose and erythropoietin treatment. Am J Gastroenterol 2009; 104: 1460–1467; doi: 10.1038/ajg.2009.114
12. Lewis JD. The utility of biomarkers in the diagnosis and therapy of inflammatory bowel disease. Gastroenterology 2011; 140: 1817-1826. doi: 10.1053/j.gastro.2010.11.058
13. Wells CW, Lewis S, Barton JR, Corbett S. Effects of changes in hemoglobin level on quality of life and cognitive function in inflammatory bowel disease patients. Inflam Bowel Dis 2006; 12: 123-130. doi: 10.1097/01.MIB.0000196646.64615.db
14. Goddard AF, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. British Society of Gastroenterology. Gut 2000; 46 (Suppl 3–4): IV1–5. doi: 10.1136/gut.46.suppl_4.iv1
15. Gisbert JP, Gomollón F. Common misconceptions in the diagnosis and management of anemia in inflammatory bowel disease. Am J Gastroenterol 2008; 103: 1299–1307. doi: 10.1111/j.1572-0241.2008.01846.x
16. 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: 1545-1553. doi: 10.1002/ibd.20285
17. Reinisch W, Chowers Y, Danese S, et al. The management of iron deficiency in inflammatory bowel disease - an online tool developed by the RAND/UCLA appropriateness method. Aliment Pharmacol Ther 2013; 38: 1109-1118. doi: 10.1111/apt.12493
18. Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. Nat Rev Gastroenterol Hepatol 2010;7:599–610. doi: 10.1038/nrgastro.2010.151
19. Lindgren S, Wikman O, Befrits R, et al. Intravenous iron sucrose is superior to oral iron sulphate for correcting anemia and restoring iron stores in IBD patients: A randomised, controlled, evaluator-blind, multicentre study. Scand J Gastroenterol 2009; 44: 838-845. doi: 10.1080/00365520902839667
20. Kulnigg S, Stoinov S, Simanenkov V, et al. A novel intravenous iron formulation for treatment of anemia in inflammatory bowel disease: the ferric carboxymaltose (FERINJECT) randomized controlled trial. Am J Gastroenterol 2008; 103: 1182–1192. doi: 10.1111/j.1572-0241.2007.01744.x
21. Khorana AA, Francis CW, Blumberg N, Culakova E, Refaai MA, Lyman GH. Blood transfusions, thrombosis, and mortality in hospitalized patients with cancer. Arch Intern Med 2008; 168: 2377–2381. doi: 10.1001/archinte.168.21.2377

22. Chen W, Lee S, Colby J, et al. The Impact of Pre-Transplant Red Blood Cell Transfusions in Renal Allograft Rejection. Rockville (MD): Agency for Healthcare Research and Quality (US): 2012, Mar 7., Report no: RENT0610.
23. Harvey AR, Basavaraju SV, Chung CW, Kuehnert MJ. Transfusion-related adverse reactions reported to the National Healthcare Safety Network Hemovigilance Module, United States, 2010 to 2012. Transfusion 2014. doi: 10.1111/trf.12918
24. Minhas V, Wood C. Epidemiology and transmission of Kaposi's sarcoma-associated herpes virus. Viruses 2014; 6: 4178-4194. doi: 10.3390/v6114178