Evolution of the prevalence and characteristics of anemia in Inflammatory Bowel Diseases between 1993 and 2003

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Abstract

Introduction : **Anemia has been considered as an overlooked complication of inflammatory bowel disease. Studies dating back to the 80ties and the 90ties have shown 30% of anemia among Inflammatory Bowel Disease patients. More recently, the broader use of immunosuppressive drug and infliximab allowing better mucosal healing as well as a more aggressive treatment of anemia, including the use of safer form of IV iron, may have influenced the prevalence of anemia among IBD patients. Our aim was to asses the prevalence and characteristics of anemia among two cohorts of IBD patients at 10 years interval and to look for associated clinical or demographic factors.**

Methods : **using the IBD patients register of one senior gastroenterologist, we identified IBD patients he had consecutively seen and who had blood test at the outpatient clinic during the years 1993 and 2003. Demographic and clinical characteristics, treatment for Crohn's disease, blood test results and treatment of anemia were recorded and compared between these two cohorts. Anemia was defined as an hemoglobin level lower than the normal value of the laboratory of our hospital.**

Results : **80 and 90 patients were identified in 1993 and 2003, respectively. There was no significant difference between the two cohorts, according to age, gender, disease type, duration or location. There were 27/80 (33.8%) and 15/90 (16.7%) anemic patients in 1993 and 2003, respectively (P = 0.013). The prevalence of severe anemia (hemoglobin level < 10.5 g/100 ml) was similar in the two cohorts (6.3% and 5.6%). Characteristics of the anemia were similar in the two cohorts with a majority of iron deficiency anemia and inflammatory anemia. Ferritin and CRP levels were not significantly different in the two cohorts. The only significant difference was a more frequent use of immunosuppressive treatment and infliximab in 2003 than in 1993 (33.3% vs. 13.8% ; P = 0.0038, RR : 0.41, 0.22-0.77)**

Conclusions : **Prevalence of mild to moderate anemia has significantly decreased in our population over the last 10 years. The only difference detected between the two cohorts was the increased use of immunosuppressive drug (mainly azathioprine).** (Acta gastroenterol. belg., **2006**, 69, **1-4**).

Key words : inflammatory bowel disease, anemia, Crohn's disease, Ulcerative colitis.

Introduction

Inflammatory bowel diseases (IBD) are heterogeneous multifactorial polygenic diseases, characterized by chronic inflammation of the gastrointestinal tract. Anemia is an overlooked complication of IBD although it has been used for more than fourty years as indicator of disease severity (1). During the past decade relevant progress has been made in the understanding and treatment of IBD-associated anemia (2), particularly concerning the role of cytokines as mediators (including interferon ß, interleukin 1 or tumor necrosis factor) (3,4,5,6,7,8) and treatment by intravenous iron and erythropoietin (9,10). The pathogenesis is dominated by iron deficiency due to intestinal blood loss, iron malabsorption, or impaired dietary intake (11,12). Intestinal inflammation may also contribute to the degree of anemia by mechanisms of anemia of chronic disease (3,4, 11). More particularly, inadequate secretion of erythropoietin (9,11,13) which is the primary factor for growth and differentiation of erythroid precursors cells (14) has also been pointed out. There are other anecdotal contributors to IBD-associated anemia such as glucose-6-phosphate deshydrogenase deficiency, auto-immune hemolysis, surgical resection of the terminal ileum, myelosuppression, vitamins B12, or folate deficiency (15).

Studies dating back to the 80ties and the 90ties have shown up to 30% of anemia among IBD patients (11,16). Anemia has significant impact on quality of life, cognitive functions, ability to work and general well-being (17). More recently, the broader use of immunosuppressive drugs and infliximab allowing better mucosal healing as well as a more aggressive treatment of anemia, including the use of safer form of intravenous iron, may have influenced the prevalence of anemia among IBD patients. The aim of our study was to asses the prevalence and characteristics of anemia among two cohorts of IBD patients at 10 years interval and to look for associated clinical or demographic factors.

Methods

Patients

From the IBD patients register of one senior gastroenterologist (JB) of our university hospital (CHU of Liège), we identified IBD patients he had consecutively seen and who had blood test at the outpatient clinic during the years 1993 and 2003. We identified 80 and 90 patients in 1993 and 2003, respectively. These two cohorts of patients were completely different, patients common to the two cohorts being systematically suppressed. The medical notes of these 170 patients were carefully retrospectively reviewed. Patients whose medical notes were incomplete were not included in the

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present study. For each one, we determined age at diagnosis, gender, disease type, duration, location (using the Vienna classification for Crohn disease (CD) (18) and classifying Ulcerative Colitis (UC) as proctitis, left colitis or pancolitis), blood test results and treatment for IBD. For each patient studied in 1993 or 2003, we only considered the first blood test performed during that year, and the clinical characteristics were recorded at the corresponding date.

Age at diagnosis, gender, disease type, duration and location of IBD were retrieved from our IBD database and the medical notes of the patients. For blood test results, we recorded : hemoglobin, mean erythrocyte volume , serum iron, ferritin, vitamin B12, folic acid, c-reactive protein, blood platelets and leucocytes. Treatments for IBD were classified in three categories : immunosuppressive drugs or biologicals (azathioprine, 6-mercaptopurine, 6-thioguanine, methotrexate, infliximab, cyclosporine), corticoids and mesalazine or sulfasalazine. Treatments recorded were thos received during the last three months before the blood test. We also tried to determine the treatment of anemia the patient had received during the year before the blood test (oral or intravenous iron, red blood cells transfusions, cobalamin or folic acid supplementation), although it was more difficult to find complete data on this point in the medical notes of the patients (particularly for oral iron, cobalamin or folic acid supplementation).

Anemia was defined as an hemoglobin (Hb) level lower than the normal value of the laboratory of our hospital (11,6 and 13 g/100 ml for women and men, respectively). Severe anemia was defined as an Hb level lower than 10,5 g/100 ml. Anemia was characterized as follow : iron deficiencies anemia (hypoferritininemia), inflammatory anemia (C-reactive protein elevated, normal or increased ferritinemia, normal cobalamin and folic acid), megaloblastic anemia (deficiciencies in cobalamin or folic acid), myelosuppression (leucocytes and platelets decreased), undetermined (blood test not complete).

All the results were compared between the two cohorts.

Expression of results and statistics

The results were expressed as proportions, percentages, means or medians as appropriate. The results were compared between groups by Mann Whitney or Fisher's exact test. P value was considered as significant when $< 0,05$.

Results

There was no significant difference between the two cohorts according to age, gender, disease type and location, disease duration and previous surgery (Table 1).

There were 27/80 (33.8%) and 15/90 (16.7%) anemic patients in 1993 and 2003, respectively ($p = 0.013$). When studying CD and UC separately, the difference was significant only in CD (Table 2). The prevalence of severe anemia was similar in the two cohorts (6.3% and 5.6%). Characteristics of the anemia were similar in the two cohorts (Table 2). Ferritin levels and c-reactive protein were not significantly different in the two cohorts (Table 2).

Table 1. — **Characteristics of the patients of the two cohorts**

	1993 (n = 80)	2003 (n = 90)
Age (yr)		
Median	33	37
Range	19-79	16-74
Sex (M/F)	31/49	34/56
Ulcerative colitis	16	17
Proctitis	2	2
Left colitis	7	12
Pancolitis	7	3
Crohn's disease	64	73
L1	15	28
L2	18	15
L3	27	25
L4	4	5
Disease duration (mo)		
Median	51	68,5
Range	1-353	1-327
Previous surgery	34	31

The only significant difference was a more frequent use of immunosuppressive treatment in 2003 than in 1993 (33.3% vs 13.8% ; $P = 0.0038$, RR : 0.41, 0.22-0.77) (Table 3). Once again this difference was essentially due to CD since no UC patient was treated with immunosuppressive drug in 1993 and only one in 2003.

Discussion

Our data show a decrease in frequency of anemia in IBD over the last decade. However the main characteristics of anemia were similar and the frequency of severe anemia has not decreased. Anemia is an important complication of IBD, associated with altered quality of life (17). Therefore, decrease in its prevalence may be considered as an improvement of the global management of these patients.

Although obtained through a retrospective study, this result may be considered as reliable.

To avoid inhomogeneity between the two compared cohorts, we used the personal IBD register of one senior gastroenterologist of our university, whose type of practice or recruitment has not dramatically changed over last decade. The changes observed can thus be considered as changes in trends for the global management of IBD in a tertiary referral centre rather than as bias of recruitment. We further could avoid selection bias by using a systematic register : all the patients seen at the outpatient clinic and who underwent blood test were included. While there was a significant decrease in global

Table 2. — **Frequency and characteristics of anemia in the two cohorts**

	1993	2003
Prevalence of anemia (n)		
Women	16/49 (severe = 3)	7/56 (severe = 3)
Men	11/31 (severe = 2)	8/34 (severe = 2)
CD	22/64	11/74*
UC	5/16	4/17
TOTAL	27/80 (severe = 5)	15/90** (severe = 5)
Ferritin level (µg/liter)		
Median	40	45,5
Range	5-448	3-280
C-reactive protein level		
Median	11,5	8
Range	0-126	1-177
Characteristics of anemia		
Iron deficiency	5	3
Inflammatory	15	7
Megaloblastic	1	0
Undetermined	6	5

* as compared to 1993 (Fischer's exact test), P = 0.009 ; ** P = 0.013.

Table 3. — **Patients treatment**

N° of patients treated	77	85
untreated	3	5
Immunosuppressive drugs	11	30*
-azathioprine	10	20
-azathioprine+infliximab	0	4
-cyclosporine	1	0
-6-thioguanine	0	1
-6-thioguanine+infliximab	0	1
-6-thioguanine and then methotrexate	0	1
-azathioprine+infliximab and then methotrexate+infliximab	0	1
-methotrexate+infliximab	0	1
-6-mercaptopurine	0	1
Corticoïds -systemic	25	25
-topic	0	16
5 ASA	63	56
Other	5	0

* 33.3% as compared to 13.8% in 1993 (Fischer's exact test), P = 0.0038, RR : 0.41, 0.22-0.77.

anemia frequency between 1993 and 2003, the frequency of severe anemia remained the same. We have no explanation for this result but the decrease in non severe anemia is already clinically relevant since decrease in quality of life and cognitive or physical performance is already observed with subnormal levels of hemoglobin (17).

The only significant difference between the two cohorts was the use of immunosuppressive drugs and infliximab which was higher in 2003. The potential for immunosuppressive drugs, particularly Azathioprine which was used in most cases in our series, and infliximab to induce mucosal healing has been clearly demonstrated (19,20). This potentially better mucosal healing in CD may be the main reason for the observed decrease in prevalence of anemia. One argument which strengthens this hypothesis is that this decrease was more prominent for CD, where increase in immunosuppressive drug use was more prominent and infliximab was introduce in some patients. Mucosal healing is also more difficult to obtain in CD than in UC, particularly with conventional drugs, including steroids and 5-ASA. Alternatively, increase in immunosuppressive use may have reflected a more severe disease in the 2003 cohorts. Seeming to substantiate this hypothesis, we also observed a trend towards an increased use of corticosteroids. However, this was only when considering topical steroids, which did not exist in 1993 and which are not necessarily prescribed for severe disease, while the use of systemic steroid was the same. Frequency of previous surgery that can also be considered as a marker of disease severity was also the same in the two cohorts. Therefore we do not think the 2003 cohorts was characterized by more severe disease, and if it had been the case, it would probably not have explained our results since we would have expected more anemia related to more severe disease. Other reasons we could not identify in our retrospective study could also have been implicated. A better nutritional approach with better alimentary iron intake may have played a role although we have no suggestion for that. A more systematic and aggressive treatment of anemia, including the use of intravenous iron may also have influenced the results. It was however difficult to find precise data in the medical notes of the patients about previous episodes of anemia and their treatment. Nevertheless, this potential change in management of anemia should also have induce a significant decrease of anemia in UC, which was not the case in our series. This last point must be interpreted with caution since our UC population was rather small.

In conclusion, we found a decrease in the prevalence of anemia in our IBD population over the last decade. The prevalence is currently around 15%. This decrease was mainly observed in CD and for moderate anemia. Factors responsible for this decrease are difficult to disclose in such retrospective study, but the increased use of immunosuppressive treatment may have played a role.

Acknowledgements

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