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Usefulness of peripheral blood monocyte count to predict relapse in patients with inflammatory bowel disease: a prospective longitudinal cohort study

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ABSTRACT

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Background: monocytes play an important role in the pathogenesis of inflammatory bowel disease but data are scarce regarding activity biomarkers, above all in patients under biologic therapies.

Objective: the aim of this study was to evaluate the value of monocyte measurements in predicting flares in inflammatory bowel disease patients under maintenance treatment with anti-TNF.

Methods: a prospective, observational cohort study was designed. Relapse was defined as a Harvey-Bradshaw score > 4 in Crohn's disease, and a partial Mayo score ≥ 2 in ulcerative colitis. Monocyte concentration was quantified at 4-month intervals for twelve months. A total of 95 consecutive patients were included. Median age was 42 years, 50.5 % were female, and 75 % had Crohn's disease.

Results: in all, 65 (68.4 %) patients remained in clinical remission. Mean monocyte count preceding a relapse was 563 (standard deviation: 144) compared to 405 (standard deviation: 177) in patients who remained in remission. Final monocyte count was significantly different between relapse and remission in Crohn's disease (0.82; 95 % CI: 0.71-0.90; $p < 0.005$). According to the multivariate analysis, only monocytes and fecal calprotectin were related to more relapses.

Conclusion: in conclusion, in inflammatory bowel disease patients under anti-TNF therapy, repeat monocyte counts could help monitor patients, at least in Crohn's disease.

Keywords: Monocytes. Relapse. Crohn's disease. Ulcerative colitis.

INTRODUCTION

Inflammatory activity is associated with the onset of symptoms and the development of complications of inflammatory bowel disease (IBD), which usually require modification of treatment. Different clinical and endoscopic indexes, as well as inflammatory biomarkers, are used to evaluate the activity of the disease (1-6). Predictors of relapse are needed to make therapeutic decisions to avoid

undertreatment as well as overtreatment.

Some biomarkers have been proposed that predict IBD relapse and they are more specific than clinical indexes as well as better tolerated and cheaper than endoscopic indexes. Blood biomarkers are commonly used, mainly erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). However, ESR and CRP are nonspecific and may be elevated in other inflammatory processes unrelated to IBD (7). Fecal biomarkers such as calprotectin (FC) are more specific and sensitive than blood biomarkers, with the main advantage of being unaffected by extraintestinal processes (8). However, FC is not always available worldwide and rapid tests are still not commonly used in clinical practice because of their cost and the need for on-demand specimen collection (9-11).

Peripheral blood monocytes play an important role in the pathogenesis of inflammatory bowel disease (12-14). Monocyte migration to tissues and differentiation to macrophages and dendritric cells is determined by the inflammatory milieu and pathogen-associated pattern recognition receptor (15). The quantification of circulating monocytes is cheaper than other biomarkers such as FC, and is available worldwide. Monocytes have been proposed as a biomarker of activity in patients with ulcerative colitis (UC), but data are scarce and information in patients with Crohn's disease (CD) under biologic therapies is lacking (16,17).

We hypothesized that the number of monocytes in peripheral blood correlates with IBD activity and can be used as predictive biomarker in IBD. The aim of the study was to evaluate the accuracy of circulating monocyte quantification to predict flares in IBD patients under maintenance treatment with anti-tumor necrosis factor (TNF) drugs.

MATERIALS AND METHODS

Design, population, and sample

A prospective, longitudinal cohort study with a 16-month follow-up was designed and performed at our IBD Unit, Department of Gastroenterology. Patients aged 18 years or older with a previous diagnosis of IBD based on clinical, endoscopic, radiological, and histological criteria were consecutively enrolled. The disease was characterized according to the Montreal classification of CD based on age at diagnosis, location, and

behavior, and UC was categorized based on the extent of disease (18). For final inclusion, patients had to be in clinical remission for at least 6 months on normal-schedule maintenance adalimumab (ADA) (40 mg every other week) or infliximab (IFX) therapy (5 mg/kg every 8 weeks). Patients receiving different doses or schedules of ADA or IFX, and those being treated with a different anti-TNF were excluded. Any antibiotic or any non-steroidal anti-inflammatory drug (NSAID) therapy within 6 months before inclusion, as well as the presence of any cardiorespiratory, liver, hematological, neurological, renal, or serious psychiatric disorders were also considered as exclusion criteria.

Data collection

Disease activity was clinically assessed at inclusion and at 4-month intervals on the day of ADA or IFX administration up to the end of the study. Relapse was defined using clinical indices (Harvey-Bradshaw index > 4 in CD and a Mayo partial index ≥ 2 in UC). Patients were screened for total white blood cell count (normal 4,000-10,000 per mm^3), monocytes (normal < 800 cells/mm^3), erythrocyte sedimentation rate (ESR, normal < 20 mm/h), serum CRP (normal < 0.8 mg/dL), and FC (normal < 100 µg/g) at inclusion and at 4-month intervals for 1 year or until relapse. The end of the study for each patient was defined either by relapse of the disease or the end of the 16-month follow-up period. Final monocyte count was measured at the end of the study in each patient.

Independent variables

Clinical and demographic characteristics of patients were recorded at inclusion: age, age at diagnosis, gender, type of IBD, disease duration, previous surgery, smoking habit, extraintestinal manifestations, concomitant immunosuppressants, previous anti-TNF therapy, duration of biological treatment, disease location (ileal, colonic or ileocolonic), and behavior (inflammatory, stenosing or fistulizing) for CD and location for UC (proctitis, left-sided colitis, or pancolitis). Total white blood cell count, monocytes, erythrocyte sedimentation rate, serum CRP, and FC were recorded at inclusion and at 4-month intervals for 1 year or until relapse.

Dependent variable

Presence of relapse, defined by a Harvey-Bradshaw index > 4 in CD and a Mayo partial index ≥ 2 in UC, was considered as dependent variable.

Statistical analysis

Continuous variables are shown as median and range. For categorical variables, the number of observations and percentages are given for each category. Comparisons between patients with flare and remission were performed using the Mann-Whitney U-test according to data distribution. The receiver-operating characteristic curve was drawn for the diagnostic accuracy analysis. The optimal cut-off value of monocyte count for the evaluation of IBD relapse was that which provided the highest sensitivity and specificity. The diagnostic sensitivity, specificity, positive predictive value, and negative predictive value of monocyte count to predict IBD relapse were calculated. A multivariate stepwise logistic regression analysis was performed to identify factors independently associated with IBD relapse. Variables with $p < 0.10$ in the univariate analysis were included in the multivariate analysis. A correlation analysis, using Spearman's rho, was used to determine the relation between FC and monocytes. Results were considered to be statistically significant at a p level below 0.05. The Statistical Package for the Social Sciences (SPSS version 19, Chicago) for Windows was used for data analysis. All authors had access to the study data, and reviewed and approved the final manuscripts

Ethical considerations

The study was approved by the Clinical Research Ethics Committee of the Galician Ministry of Health (Comité de Ética de Investigación Clínica de Galicia, Consellería de Sanidad, www.ceic.sergas.es) with approval number 2012/431. All patients provided their written informed consent for the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study was performed in accordance with the Declaration of Helsinki and its amendments, and the Good Clinical Practice guidelines.

RESULTS

A total of 106 consecutive patients that fulfilled the inclusion criteria were included in the study. Eleven were lost to follow-up, thus 95 patients were considered for the final analysis (50.5 % female; median age, 42 years; range, 18 to 78 years). Twenty-two (23.2 %) patients were on concomitant immunosuppressant therapy (1 with methotrexate and 21 with azathioprine). The patients' clinical and sociodemographic characteristics are shown in table 1. Sixteen months after inclusion, 65 (68.4 %) patients remained in clinical remission, whereas disease relapse occurred in the remaining 30 (31.6 %) patients.

The mean number of circulating monocytes was 563 cells/mm^3 (95 % confidence interval: 497-629 cells/mm^3) in patients who had a disease relapse over the following 4 months after measurement, and 405 cells/mm^3 (95 % confidence interval: 369-440 cells/mm^3) in those in clinical remission ($p < 0.005$). These differences were present in CD, but not in UC patients. The differences between CD and UC patients are shown in table 2.

Final monocyte counts significantly differed between relapse and remission (area under curve (AUC): 0.762; 95 % confidence interval: 0.663-0.843; $p < 0.005$) (Fig. 1). By applying a cutoff point of 350 cells/mm^3, the test had a sensitivity of 93.3 %, a specificity of 42.3 %, a positive predictive value (PPV) of 63 %, and a negative predictive value (NPV) of 92.7 % for the prediction of relapse over the following 4 months (Table 3). When the cutoff point was set at > 800 cells/mm^3, the sensitivity and specificity to predict IBD relapse was 16.7 % and 100 %, respectively (positive and negative predictive values of 100 % and 71.8 %, respectively).

FC (OR: 1.006; CI: 1.003-1.010, $p < 0.005$) and monocytes (OR: 1.007; CI: 1.002-1.012, $p = 0.004$) were the only two independent variables significantly and independently associated with IBD relapse in the multivariate analysis. The correlation coefficient of FC and monocytes was $r = 0.304$; $p = 0.003$. In CD, the correlation coefficient was $r = 0.357$; $p = 0.002$.

DISCUSSION

This prospective study shows that the number of circulating monocytes may allow the exclusion of clinical relapse over the following 4 months in patients with IBD on maintenance treatment with anti-TNF drugs. White blood cells are routinely checked during clinical visits and have been evaluated as biomarkers in IBD, but data related to monocytes are scarce. As far as we know, only two previous studies have showed that UC patients with monocytosis have more severe disease, increased complications, and more healthcare use. This association is independent of age, disease duration, and treatment (15-17,19,20).

Monocytosis has been associated with chronic infections such as tuberculosis and endocarditis as well as myeloproliferative and rheumatic disorders and artherosclerosis (21-24). Monocytes can help identify tuberculosis infection and disease stages (21). Monocyte to high-density lipoprotein cholesterol ratio is associated with in-hospital and long-term death in patients with infectious endocarditis (22). Monocytes are important for all stages of atherosclerosis, but the role of each subset in various stages of disease is still unresolved (23-25). Patients with rheumatoid arthritis of a short duration have increased total monocytosis and alterations in peripheral blood monocytes, in spite of the fact that there is no evidence of subclinical atherosclerosis (26). Therefore, the activation of the innate immune system seems to be associated with critical illness and could explain the role of monocytes in IBD.

Endoscopic indexes could be considered as the gold standard to predict IBD relapse due to their high sensitivity and specificity. However, colonoscopy is invasive, expensive and not always a well-tolerated technique (5,6). Some biomarkers have been proposed to predict IBD relapse, which are more specific than clinical indexes and better tolerated and cheaper than endoscopic indexes. Blood biomarkers are commonly used in clinical practice, mainly CRP. Fecal markers such as FC are more specific than blood markers, but are also more expensive and not available in all hospitals. In our cohort, monocytes were found to be more effective than CRP and ESR. Moreover, the determination of monocytes is cheaper than other biomarkers and is available in less than one day, but with a lower sensitivity and specificity than FC. Thus, monocytes can be an alternative in hospitals where FC is not easily available or

when patients do not want or forget to provide a stool sample.

Patients under biological treatment typically have more severe disease. The use of biomarkers in this setting can be useful to monitor patients and to optimize treatment. Although up to 800 circulating monocytes/mm^3 are considered normal, a monocyte count higher than 350 cells/mm^3 was the best cut-off to predict relapse in the present study. If 800 cells/ mm^3 is used as the cut-off, the sensitivity to predict IBD relapse is too low to be useful in clinical practice. The negative predictive value of the test is good, so the test could exclude relapse if negative. We interpreted with caution the difference between UC and CD given the relatively small sample size of UC patients.

Previous studies have demonstrated a good correlation between FC and clinical and endoscopic activity (27-34). However, this is the first prospective study showing that monocytes are also good predictors of activity in CD patients under anti-TNF biological treatment, and above all can exclude relapse. In UC, the values appear to be different and the AUC was not so good, thus limiting the applicability of the test in patients with UC, although the small sample size of UC patients means that definitive conclusions cannot be drawn with confidence. In CD, the correlation coefficient of FC and monocytes was 0.357. Thus, an r of 0.357 is a fair correlation with very high statistical significance.

The prospective longitudinal design, the long-term follow-up, and the repeated measurement of inflammatory markers such as leukocytes, FC, ESR, and CRP are the strengths of the present study. On the contrary, the use of clinical scores to define remission instead of mucosal healing was the main limitation. Colonoscopy was performed only when clinically indicated, and not in patients in clinical remission. We do not know the efficacy of monocytes as a predictor of relapse in patients with cardiorespiratory, liver, hematological, neurological, renal, or serious psychiatric disorders, because the presence of these illnesses was considered exclusion criteria. Finally, the small sample size of UC patients led us to interpret the results with caution.

In conclusion, the present study shows that monocytes allow the monitoring of patients with IBD under maintenance anti-TNF therapy, at least in CD. Monocytes can be a cost-effective and accessible complementary method to monitor patients with CD.

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Table 1. Clinical and sociodemographic data

	Inflammatory bowel disease n = 95	**Crohn's disease n = 71**	**Ulcerative colitis n = 24**
Age (years), median (range)	42 (18-78)	42 (18-78)	44 (22-76)
Age at diagnosis (years), median (range)	32 (13-72)	32 (13-72)	32 (18-54)
Gender, n (% of females)	48 (50.5)	36 (50.7)	12 (50)
Disease duration (years), median (range)	9.4 (1-23)	9 (1-23)	10 (2-22)
Previous surgery, n (%)	30 (31.6)	28 (39.4)	2 (8.3)
Smoker, n (%)			
Current	17 (17.9)	15 (21.1)	2 (8.3)
Never	56 (58.9)	38 (53.5)	18 (75)
Former	22 (23.2)	18 (25.4)	4 (16.7)
Extraintestinal manifestations, n (%)	21 (22.1)	16 (22.5)	5 (20.8)
Concomitant immunosuppressant, n (%)	22 (23.2)	16 (22.5)	6 (25)
Infliximab, n (%)	61 (64.1)	40 (56.3)	21 (87.5)
Adalimumab, n (%)	34 (35.9)	31 (43.7)	3 (12.5)
At least one previous anti-tumor necrosis factor, n (%)	13 (13.7)	12 (16.9)	1 (4.2)
Behavior of Crohn's disease, N (%)			
Inflammatory		4 (5.6)	
Stenosing		31 (43.7)	
Fistulizing		36 (50.7)	
Disease location, N (%)			
Ileitis		26 (36.6)	
Ileocolitis		7 (9.9)	
Colitis		38 (53.5)	
Extensive colitis			14 (58.3)
Left colitis			10 (41.7)

Table 2. Mean number of circulating monocytes in patients with relapse

	Ulcerative colitis (24)			Crohn's disease (71)		
	Relapse	Remission	p-value	Relapse	Remission	p-value
Mean monocyte count (95 % CI)	475 (315-635)	381 (290-473)	> 0.05	596 (522-668)	412 (374-451)	< 0.005

CI: confidence interval.

Table 3. Sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of monocytes to predict relapse

	Cutoff	**AUC (95 % CI)**	**S**	**Sp**	**PPV**	**NPV**
Inflammatory bowel disease patients (95)	> 350	0.76 (0.66-0.84)	93.3	40	42.3	92.7
Crohn's disease patients (71)	> 350	0.82 (0.71-0.90)	100	36.7	42.6	100
Ulcerative colitis patients (24)	> 250	0.63 (0.41-0.82)	100	12.5	35	100

S: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value.