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**USEFULNESS OF PERIPHERAL BLOOD MONOCYTE COUNT
TO PREDICT RELAPSE IN PATIENTS WITH INFLAMMATORY
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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

Monocytes play an important role in the pathogenesis of inflammatory bowel disease but data are scarce as a biomarker of activity, above all, in patients under biologic therapies. The aim was to evaluate the value of monocyte measurements in predicting flares in inflammatory bowel disease patients under maintenance treatment with anti-TNF. 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. Monocytes concentration was quantified at 4-month intervals for twelve months. 95 consecutive patients were included. The median age was 42 years, 50.5% female and 75% with Crohn’s disease. 65 (68.4%) patients remained in clinical remission. Mean monocyte concentration preceding the relapse was 563 (standard deviation 144) compared to 405 (standard deviation 177) in patients who kept in remission. Final monocytes concentration significantly differentiated between relapse and remission in Crohn’s disease (0.82; 95% CI: 0.71-0.90; P <0.005). In the multivariate analysis, only monocytes and fecal calprotectin related to more relapses. In conclusion, in inflammatory bowel disease patients under anti-TNF therapy, repeated monocytes concentration could help in order to monitoring patients, at least,

in Crohn's disease.

Abbreviations

Adalimumab = ADA; C- reactive protein = CRP; Crohn,'s disease = CD; Erythrocyte sedimentation rate = ESR; Fecal calprotectin = FC; Inflammatory bowel disease = IBD; Infliximab = IFX; Non-steroidal anti-inflammatory drugs= NSAID; Tumor necrosis factor = TNF; Ulcerative colitis = UC

Keywords

Monocytes, Relapse, Crohn's disease, Ulcerative colitis.

INTRODUCTION

The 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 necessary to make therapeutic decisions to avoid undertreatment as well as overtreatment.

Some biomarkers have been proposed to predict IBD relapse and they are more specific than clinical indexes and 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 can 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 the 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 dendritic cells is determined by the inflammatory milieu and pathogen associated pattern recognition receptor. [15 Quantification of circulating

monocytes is cheaper than other biomarkers 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) and 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 predictor 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 16-month follow-up was designed and conducted at our IBD Unit of the Department of Gastroenterology.

Patients aged 18 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 behaviour, and that of UC based on the extent of the 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 the 6 months before inclusion, as well as the presence of any cardiorespiratory, liver, haematological, neurological, renal, or serious psychiatric disorders, were also considered as exclusion criteria.

Data collection

Disease activity was clinically assessed at inclusion and at 4 months 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 4000-10000 mm³),

monocytes (normal <800 cells/mm³), 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. End of the study in each patient was defined either by the relapse of the disease or the end of the 16-month follow-up period. Final monocytes count is that 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 diagnose, 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 behaviour (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 as defined by a Harvey-Bradshaw index >4 in CD and a Mayo partial index ≥ 2 in UC was considered as the 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 diagnostic-accuracy analysis. The optimal cut-off value of monocytes count for the evaluation of IBD relapse was that providing the highest sensitivity and specificity. Diagnostic sensitivity, specificity, positive predictive value and negative predictive value of monocytes count to predict IBD relapse were calculated. Multivariate stepwise logistic regression analysis was performed to identify factors independently associated with IBD relapse. Variables with $p < 0.10$ in univariate analysis

were included in the multivariate analysis. We performed correlation analysis, Spearman's rho, to know the relation between FC and monocytes. Results were considered to be statistically significant at a p level below 0.05. 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 have 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 the approval number 2012/431. All patients provided written informed consent to the study. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. The study was conducted in accordance with the Declaration of Helsinki and its amendments, and Good Clinical Practice guidelines.

RESULTS

A total of 106 consecutive patients fulfilling inclusion criteria were included. Eleven of them were lost over follow-up, thus 95 patients were considered for 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 methotrexate and 21 azathioprine). Patients' clinical and sociodemographic characteristics are shown in table 1. Sixteen months after inclusion, 65 (68.4%) patients remained in clinical remission, whereas the disease relapsed in the remaining 30 (31.6%) patients.

Mean number of circulating monocytes was 563 cells/mm³ (95% confidence interval 497-629 cells/mm³) in patients who had a relapse of the disease over the following 4 months from the measurement and 405 cells/mm³ (95% confidence interval 369-440 cells/mm³) 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 differentiated between relapse and remission (area under curve (AUC) 0.762; 95% confidence interval: 0.663-0.843; $P < 0.005$; Figure 1). By applying a cutoff point of 350 cells/mm³, the test has a sensitivity of 93.3%, specificity 42.3%, positive predictive value (PPV) 63% and negative predictive value (NPV) 92.7% for the prediction of relapse over the following 4 months (Table 3). When the cutoff point was set at > 800 cells/mm³ 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; IC 1.003-1.010, $P < 0.005$) and monocytes (OR 1,007; IC 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 excluding 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 are scarce related to monocytes. As far as we know, only two previous studies have showed that UC patients with monocytosis have more severe disease, increased complications and healthcare utilization. This association is independent of age, disease duration and treatment [15-17, 19-20].

Monocytosis has been associated with chronic infections such tuberculosis and endocarditis as well as myeloproliferative and rheumatic disorders and arteriosclerosis [21-24]. Monocytes can help identifying 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 diseases is still unresolved [23-25]. Patients with rheumatoid arthritis of short duration present increased total monocytosis and

alteration in peripheral blood monocyte 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 it 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, but colonoscopy is invasive, expensive and not always 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 the hospitals. In our cohort, monocytes were found 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 lower sensitivity and specificity than FC. For that reason, monocytes can be an alternative in hospitals where FC is not easily available or in case patients doesn't want or forget to provide a stool sample.

Patients under biological treatment are typically patients with more severe disease. The use of biomarkers in this setting can be useful to monitor patients and to optimize the treatment.

Although up to 800 circulating monocytes/mm³ are considered normal, a count monocytes count higher than 350 cells/mm³ was the best cut-off to predict relapse in the present study. If 800 cells/mm³ is used as the cut-off, the sensitivity of the test 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 be able, if negative, to exclude a relapse. 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], but this is the first prospective study reporting that monocytes are also good predictors of activity in CD patients under anti-TNF biological treatment, and above all, can exclude a 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 lead to draw any definitive conclusion with low confidence. In CD, the correlation coefficient of FC and monocytes was 0.357. This r of 0.357 is fair correlation with very high statistical significance.

The prospective longitudinal design, the long-term follow up, 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 just if clinically indicated, and not in patients in clinical remission. We do not know the efficacy of monocytes as predictor of relapse in patients with cardiorespiratory, liver, haematological, neurological, renal or serious psychiatric disorders, because the presence of these illness was considered as a exclusion criteria. Finally, the small sample size of UC patients lead to interpret results with caution.

In conclusion, the present study shows that monocytes allows monitoring 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.

CONFLICTS OF INTEREST

RFI has served as a speaker, a consultant and advisory member for or has received research funding from MSD, Abbvie, Palex, Takeda, Janssen, Pfizer, Shire Pharmaceuticals, Dr. Falk Pharma, Casenrecordati and Tillotts Pharma.

MBA has served as a speaker, a consultant and advisory member for or has received research funding from MSD, Abbvie, Celltrion, Takeda, Janssen, Pfizer, Ferring, Faes Farma, Shire Pharmaceuticals, Dr. Falk Pharma, Chiesi, Gebro Pharma, Roche, Otsuka Pharmaceuticals and Tillotts Pharma.

JLD has no conflict of interest relevant to the manuscript to disclose.

IBR has served as a speaker, a consultant and advisory member for or has received research funding from MSD and Janssen.

JEDM has no conflict of interest relevant to the manuscript to disclose.

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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 (% 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 (%)			
Concomitant immunosuppressant , N (%)	21 (22.1)	16 (22.5)	5 (20.8)
Infliximab , N (%)	22 (23.2)	16 (22.5)	6 (25)
Adalimumab , N (%)	61 (64.1)	40 (56.3)	21 (87.5)
At least one previous anti-tumor necrosis factor , N (%)	34 (35.9)	31 (43.7)	3 (12.5)
Behavior Crohn's disease , N (%)			
Inflammatory	13 (13.7)	12 (16.9)	1 (4.2)

Stenosing			
Fistulising		4 (5.6)	
Disease location, N (%)		31 (43.7)	
Ileitis		36 (50.7)	
Ileocolitis			
Colitis		26 (36.6)	
Extense colitis		7 (9.9)	
Left colitis		38 (53.5)	14 (58.3)
			10 (41.7)

Table 2. Mean number of circulating monocytes in patients who had a relapse of the disease

	Ulcerative colitis (24)			Crohn's disease (71)		
	Relapse	Remission	p-value	Relapse	Remission	p-value
Mean Monocytes (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 in predicting relapse

	Cutoff	AUC (95%IC)	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

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