Inflammatory Bowel Diseases, 2022, **XX**, 1–8
https://doi.org/10.1093/ibd/izac044
Advance access publication 11 March 2022
Original Research Articles - Clinical

Prognostic Value of Colonic Tissue and Blood Eosinophils in Ulcerative Colitis

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Background: It has been suggested that eosinophils may be a prognostic marker of disease outcome in ulcerative colitis (UC), but conflicting data exist. The objective was to investigate the extent of mucosal eosinophils and peripheral blood eosinophil count in newly diagnosed UC patients and to investigate its predictive value in short- and long-term disease outcomes.

Methods: The degree of eosinophilia in baseline colonic biopsies and blood of newly diagnosed UC patients was retrospectively analyzed. It was investigated if tissue and blood eosinophilia could be a marker of a severe phenotype of UC, defined as the need for corticosteroids or immunomodulators in the first year or treatment with therapeutic monoclonal antibodies or colectomy during follow-up. Time to therapeutic monoclonal antibodies and time to colectomy were also evaluated as outcomes.

Results: There were 103 UC patients (median age 26 years) included. Median tissue peak eosinophil count (PEC) was 70.0 and median peripheral blood eosinophil count was 0.3 × 10^9/L at diagnosis. Tissue PEC (r = -0.161, P = .104) and blood eosinophil count (r = 0.022, P = .877) were not correlated with the severity of histologic inflammation. Logistic regression analyses did not identify PEC and blood eosinophil count as predictors of more severe disease outcomes. Tissue PEC and peripheral blood eosinophil count did not predict the time the initiation of therapeutic monoclonal antibodies or colectomy.

Conclusion: Baseline tissue or peripheral blood eosinophils are not markers of disease activity and cannot be used as a predictor of severe disease outcomes in both adults and children with UC.

Lay Summary

Baseline tissue or peripheral blood eosinophils are not markers of disease activity and cannot be used as a predictor of severe disease outcomes in both adults and children with ulcerative colitis.

Key Words: ulcerative colitis, eosinophils, colonic tissue, peripheral blood, disease activity, disease outcomes

INTRODUCTION

Ulcerative colitis (UC) is an chronic inflammatory disease of the colonic mucosa. The rectum is commonly affected, but inflammation can involve the entire colon.[1] The clinical course of UC is characterized by relapsing periods of active inflammation, defined by the presence of neutrophils in epithelium.[2] However, also increased number of eosinophils are often recognized and this suggests a potential role for these cells in UC as well.[3]

Eosinophils are normally present in the intestinal mucosal and play a role in the protective mucosal barrier of gastrointestinal tract.[4] The incidence of eosinophilic gastrointestinal disorders, such as eosinophilic esophagitis and eosinophilic gastroenteritis, is rising in the Western countries.[5,6] This resulted into renewed attention toward the role of eosinophils in other inflammatory disorders of the gastrointestinal tract, especially UC. Most research suggests a proinflammatory role for eosinophils in UC,[7] and several studies have suggested a relation between degree of tissue eosinophilia and disease activity.[8-10]

In the ongoing search for prognostic baseline parameters of a more severe disease course, mucosal and peripheral blood eosinophils have been explored as potential markers. In a pediatric cohort, both tissue and peripheral blood eosinophilia were associated with short-term need of corticosteroid treatment.[11] In adults, tissue eosinophilia during active phase of the disease was associated with a poor response to first-line treatment consisting of mesalazine and corticosteroids[12] and clinical nonresponse to vedolizumab at 6 months.[13] Tissue eosinophilia is also associated with a higher relapse rate in patients with UC in clinical and endoscopic remission.[14] However, other studies found the opposite; in both a pediatric cohorts and 2 adult patient cohorts a scarcity of tissue eosinophils was associated with more severe disease that needed treatment escalation.[15-17] Peripheral blood eosinophilia during the disease course has been linked to a more severe disease

Received for publication: January 14, 2022. Editorial Decision: February 9, 2022

development characterized by frequent use of corticosteroids, biological use, hospitalizations, and UC-related surgery.[18-20] Therefore, the literature suggests that tissue and blood eosinophils could be a potential prognostic marker of either less or more severe disease outcomes.

Considering the conflicting data, more research is clearly needed in order to determine if tissue and peripheral blood eosinophils can be used as prognostic markers in UC.[21] Therefore, the objective of this study was to investigate the extent of tissue eosinophils and peripheral blood eosinophil count in a large sample of newly diagnosed UC patients and its association with endoscopic and histologic disease activity. Furthermore, to determine the prognostic value of tissue eosinophils and peripheral blood eosinophil count in short- and long-term disease outcomes.

METHODS

Study Design and Population

This study was a retrospective cohort study. After selection of an initial cohort using the pathology databases of the Amsterdam UMC, a retrospective chart review was performed to select newly diagnosed UC patients between 2005 and 2015. Patients were included if they were newly diagnosed according to accepted criteria[1] and at least 3 years of clinical follow-up was available. Patients were excluded if they already received any form of treatment for UC at biopsy procurement, if there was uncertainty about UC diagnosis, if there was proven other cause for colorectal eosinophilia, if there was recent use of nonsteroidal anti-inflammatory drugs including 5-aminosalicylic acid or salicylic acid formulas, or if there was positive stool for ova and parasites. Eventually, after screening for eligibility, a total of 103 newly diagnosed consecutive UC patients were included (Supplementary Figure 1).

Given the retrospective nature of this study, the Dutch Medical Research Involving Human Subjects Act did not apply. A waiver for formal approval was issued by the local Institutional Review Board (W19_369#19.433). The patients selected for data extraction were offered the possibility to object against the use of their personal data for the purpose of this study.

Histology

An expert gastrointestinal pathologist blinded to patient data assessed the extent of eosinophil infiltration in the available biopsies. The biopsy with the highest degree of histological disease activity was selected for analysis. A region of interest was selected based on the location of highest eosinophil density. In this region of interest (0.23 mm^2), peak eosinophil count (PEC) was determined by counting all eosinophils. To assess if PEC merely reflected the level of active inflammation, the Geboes score was determined in parallel.[22] The Geboes scores were converted to a continuous scale (0-22) for the use as a continuous variable, as previously described.[23]

Laboratory

For the analysis of peripheral blood eosinophil count, patients were analyzed who had a complete blood count done including an eosinophil count at the time of the endoscopy or 3 months prior. If medical treatment had not been started directly after endoscopy, a blood count was also included after endoscopy until treatment was started. Peripheral blood eosinophilia was defined as an absolute eosinophilic count $>0.5 \times 10^9$/L.

Data Analysis

Statistical analysis was performed in SPSS version 25 (IBM Corp, Armonk, NY, USA). Normally distributed continuous numerical variables were described as means ± SD. Non-normal distributed variables were described as median (interquartile range [IQR]). Categorical variables were expressed as absolute and relative frequencies.

The following outcomes were evaluated: the initiation of corticosteroids in first year, the initiation of immunomodulators in first year, number of disease flares, the initiation of therapeutic monoclonal antibodies, and colectomy. A more severe disease course of UC was also defined as an outcome, which included patients who received either systemic corticosteroids or immunomodulators in the first year, or who received therapeutic monoclonal antibodies or underwent a colectomy during entire follow-up. Time to therapeutic monoclonal antibodies and time to colectomy were also evaluated as outcomes.

A Spearman's rank order correlation test was used for the correlation between PEC and the Geboes score. It was also used to analyze the correlation between PEC or blood eosinophil count and the number of flares in the first year. The Mann-Whitney *U* test was used to compare the PEC and blood eosinophil count between groups divided according to the different outcomes. Univariate logistic regression was used to analyze whether PEC or blood eosinophil count could predict the aforementioned binary outcomes. Time-to-event analyses were performed to analyze the association between PEC or blood eosinophil count and time to initiation of therapeutic monoclonal antibodies or colectomy. $P < .05$ was considered to be statistically significant.

RESULTS

A total of 103 newly diagnosed consecutive UC patients with a median age at diagnosis of 26 years and mean follow-up of 6.8 years were included. Baseline characteristics of the study population are presented in Table 1. The majority of the population consisted of patients with a pancolitis (46.1%), and only 20.6% suffered from ulcerative proctitis. Baseline peripheral blood eosinophil count was available for 53 patients. One-third of these patients showed blood eosinophilia.

Peak Eosinophil Count

The correlation between PEC and the levels of both histologic and endoscopic disease severity was assessed. Spearman's rank order correlation test was conducted to determine the relationship between PEC and the continuous Geboes score, as a measure of histologic inflammation. There was no correlation found (r = -0.161, n = 103, P = .104) (Supplementary Figure 2). No difference was found in PEC between mild and moderate-to-severe endoscopic severity (Mayo score 1 vs Mayo score 2-3: 70 [IQR, 50-110] vs 70 [IQR, 50-110]; P = .949).

The cohort was divided into a more severe disease course (n = 49) and a less severe disease course (n = 54). No differences in baseline characteristics between the 2 groups were observed (Table 1). When comparing PEC between these 2 groups, a significant difference could not be found (P = .229).

Table 1. Patient characteristics

Patient Characteristics (n = 103)	Total Population	More Severe Disease Course (n = 49)	Less Severe disease Course (n = 54)	*P* Value
Age at diagnosis, y	26 (15-43)	22 (13-42)	29 (18-43)	.079
Male	52 (51)	24 (49)	28 (52)	.771
Smoking	5 (5)	3 (6)	2 (4)	.568
Follow-up, y	7 ± 3.4	6.4 ± 3.7	7.1 ± 3.1	.284
History of allergic disease				
Hay fever	3 (3)	3 (6)	0 (0)	.065
Montreal disease extent				
E1 Ulcerative proctitis	21 (20)	8 (16)	13 (24)	.330
E2 Left-sided UC	34 (33)	19 (39)	15 (28)	.236
E3 Extensive UC	48 (47)	22 (45)	26 (48)	.741
Mayo score, endoscopic				
0 Normal or inactive disease	0 (0)	0 (0)	0 (0)	
1 Mild disease	45 (44)	17 (35)	28 (52)	.080
2 Moderate disease	35 (34)	20 (41)	15 (28)	.163
3 Severe disease	23 (22)	12 (25)	11 (20)	.616
Biopsy with most severe inflammation				
Rectum	26 (25)	11 (22)	15 (28)	.534
Sigmoid	33 (32)	20 (41)	13 (24)	.069
Left side	4 (4)	2 (4)	2 (4)	.921
Descendens	5 (5)	3 (6)	2 (4)	.588
Transversum	3 (3)	2 (4)	1 (2)	.502
Ascendens	2 (2)	1 (2)	1 (2)	.945
Coecum	3 (3)	0 (0)	3 (6)	.094
Unknown origin	27 (26)	10 (20)	17 (32)	.202
PEC	70(50-110)	70 (45-105)	80 (50-120)	.229
Geboes score on continuous scale	17(16-19)	17 (16-19)	17 (16-18)	.640
Laboratory results				
Hemoglobin (n = 82), mmol/L	7.8 (7.0-8.4)	7.5 (6.9-8.4)	8.1 (7.0-8-6)	.267
CRP (n = 69), mg/L	3.0 (1.6-18.5)	8.0 (2.0-31.8)	2.6 (1.0-12.5)	.084
Leukocytes × 10^9/L (n = 80)	8.8 (6.4-11.6)	9.3 (7.3-12.0)	7.3 (5.7-10.9)	.051
Eosinophil count × 10^9/L (n = 53)	0.3 (0.2-0.7)	0.4 (0.2-0.8)	0.3 (0.1-0.4)	.100
ESR (n = 56), mm/h	17.0 (9.3-31.8)	18.0 (10.3-32.5)	16.0 (6.3-29.8)	.253
Albumin (n = 45), g/L	39.1 (36.0-44.0)	40.0 (36.5-44.3)	39.1 (35.3-43.8)	.473
Calprotectin (n = 18), mg/kg	1182.6 (512.0-2345.0)	1460.0 (892.5-2580.0)	469.0 (226.8-2205.0)	.083
Peripheral blood eosinophilia	17(32)	10 (42)	7 (24)	.174
Corticosteroids first year	40 (39)	40 (82)	0 (0)	—
Immunomodulator first year	27 (26)	27 (55)	0 (0)	—
Therapeutic monoclonal antibodies	31 (30)	31 (63)	0 (0)	—
Colectomy during follow-up	15 (15)	15 (31)	0 (0)	—

Values are median (interquartile range), n (%), or mean ± SD.
Abbreviations: CRP, C-reactive protein; E, extent; ESR, erythrocyte sedimentation rate; PEC, peak eosinophil count; UC, ulcerative colitis.
[a]A more severe disease course included patients who received either systemic corticosteroids or immunomodulators in the first year or who received therapeutic monoclonal antibodies or underwent a colectomy during entire follow-up.

There were also no significant differences in PEC found for other outcomes (Table 2). No significant correlation was present between number of flares in the first year and PEC (r_s = -0.096, n = 103, *P* = .333). Also with a logistic regression model PEC could not be identified as predictor of any of the outcomes (Table 2).

Kaplan-Meier survival analyses were conducted in order to investigate if PEC predicted the time to initiation of therapeutic monoclonal antibodies or colectomy, after creation of "low" and "high" groups according to median cutoff point (median PEC 70) in order to perform a log-rank test (Figure 1). A median time to event could not be calculated, as <50% of the patients ultimately received therapeutic monoclonal antibodies or underwent a colectomy, but no difference in time to initiation of therapeutic monoclonal antibodies (χ^2_1 = 0.159, *P* = .690) or colectomy (χ^2_1 = 0.674, *P* = .412) was found.

To quantify the influence of PEC on the time to initiation of therapeutic monoclonal antibodies or colectomy, univariate

Table 2. The associations between PEC and peripheral blood eosinophil count and disease outcomes

Outcomes	PEC				Peripheral Blood Eosinophil Count			
	Yes	No	*P* Value	Hazard Ratio (95%CI)	*P* Value	Yes × 10^9/L	No × 10^9/L	*P* Value	Hazard Ratio (95%CI)	*P* Value
A more severe disease course[a]	70 (45-105)	80 (50-120)	.229	0.90 (0.90-1.00)	.295	0.41 (0.20-0.83)	0.26 (0.15-0.43)	.100	1.22 (0.48-3.10)	.675
Therapeutic monoclonal antibodies during follow-up	70 (50-110)	70 (50-110)	.917	1.00 (0.90-1.00)	.920	0.43 (0.20-0.96)	0.28 (0.15-0.56)	.076	1.54 (0.59-4.02)	.375
Colectomy during follow-up	60 (40-80)	70 (50-110)	.523	1.00 (0.90-1.00)	.930	0.35 (0.23-1.06)	0.28 (0.15-0.63)	.275	1.36 (0.45-4.13)	.585
Corticosteroids treatment first year	65 (43-98)	80 (50-120)	.166	0.90 (0.90-1.00)	.293	0.41 (0.23-0.88)	0.25 (0.14-0.42)	.042[b]	1.45 (0.56-3.76)	.442
Immunomodulator treatment first year	60 (40-80)	80 (50-120)	.075	0.90 (0.90-1.00)	.162	0.41 (0.22-0.96)	0.27 (0.15-0.56)	.094	1.49 (0.57-3.86)	.414

Values are median (interquartile range), unless otherwise indicated. Univariate logistic regression was used to analyze whether PEC or peripheral blood eosinophil count could predict the disease outcomes.
Abbreviations: CI, confidence interval; PEC, peak eosinophil count.
[a]A more severe disease course included patients who received either systemic corticosteroids or immunomodulators in the first year or who received therapeutic monoclonal antibodies or underwent a colectomy during entire follow-up.
[b]*P* value of < 0.05, indicating a significant outcome..

Cox regression analyses were performed. They showed that PEC did not influence the time to initiation of therapeutic monoclonal antibodies (hazard ratio [HR], 0.996; 95% confidence interval [CI], 0.988-1.003; *P* = .267) or colectomy (HR, 0.999; 95% CI, 0.992-1.007; *P* = .886).

Peripheral Blood Eosinophil Counts

There was no correlation between tissue PEC and peripheral blood eosinophil count (r_{s8} = 0.266, n = 53, *P* = .054). No correlation was found between the peripheral blood eosinophil count and the continuous Geboes score (r_{s53} = 0.022, *P* = .877). No difference was found in the peripheral blood eosinophil count between mild and moderate-to-severe endoscopic severity (Mayo score 1 vs Mayo score 2-3: 0.2 [IQR, 0.1-0.4] × 10^9/L vs 0.3 [IQR, 0.2-0.8] × 10^9/L; *P* = .072).

There was no difference in the degree of peripheral blood eosinophil count between a more severe disease course (n = 24) and a less severe disease course (n = 29) (*P* = .100). Peripheral blood eosinophil count was significantly higher in those patients starting with use of corticosteroids in the first year (*P* = .042), but no differences were found in the peripheral blood eosinophil count for the other outcomes (Table 2). No correlation was found between the peripheral blood eosinophil count and the number of flares in the first year (r_s = 0.217, n = 53, *P* = .119). Also, with a logistic regression model, the peripheral blood eosinophil count could not be identified as predictor of any of the disease outcomes (Table 2).

Kaplan-Meier survival analyses were conducted in order to investigate if the baseline peripheral blood eosinophil count predicted the time to initiation of therapeutic monoclonal antibodies or colectomy, after creation of low blood eosinophil count and high blood eosinophil count groups according to cutoff point of 0.5 × 10^9/L in order to perform a log-rank test (Figure 2). A median time to event could not be calculated, as <50% of the patients ultimately received therapeutic monoclonal antibodies or underwent a colectomy, but no difference in time to initiation of therapeutic monoclonal antibodies (χ^2_1 = 0.710, *P* = .399) or colectomy (χ^2_1 = 0.091, *P* = .763) was found.

To quantify the influence of peripheral blood eosinophil count on the time to initiation of therapeutic monoclonal antibodies or colectomy, univariate Cox regression analyses were performed. They showed that the peripheral blood eosinophil count did not influence the time to initiation of therapeutic monoclonal antibodies (HR, 1.175; 95% CI, 0.619-2.230; *P* = .623) or colectomy (HR, 1.224; 95% CI, 0.478-3.133; *P* = .673).

Pediatric Part of the Cohort

After analyzing the pediatric part of the cohort separately, no difference in PEC was found between a more severe disease course (n = 21) and a less severe disease course (n = 13) (*P* = .735). No differences were found in PEC for the other outcomes (Table 3). No correlation was found between PEC and the number of flares in the first year (r_s = 0.095, n = 34, *P* = .593). Logistic regression could not identify PEC as predictor of any of the disease outcomes (Table 3)

Kaplan-Meier survival analyses were conducted in order to investigate if PEC predicted the time to initiation of therapeutic monoclonal antibodies or colectomy, after creation of

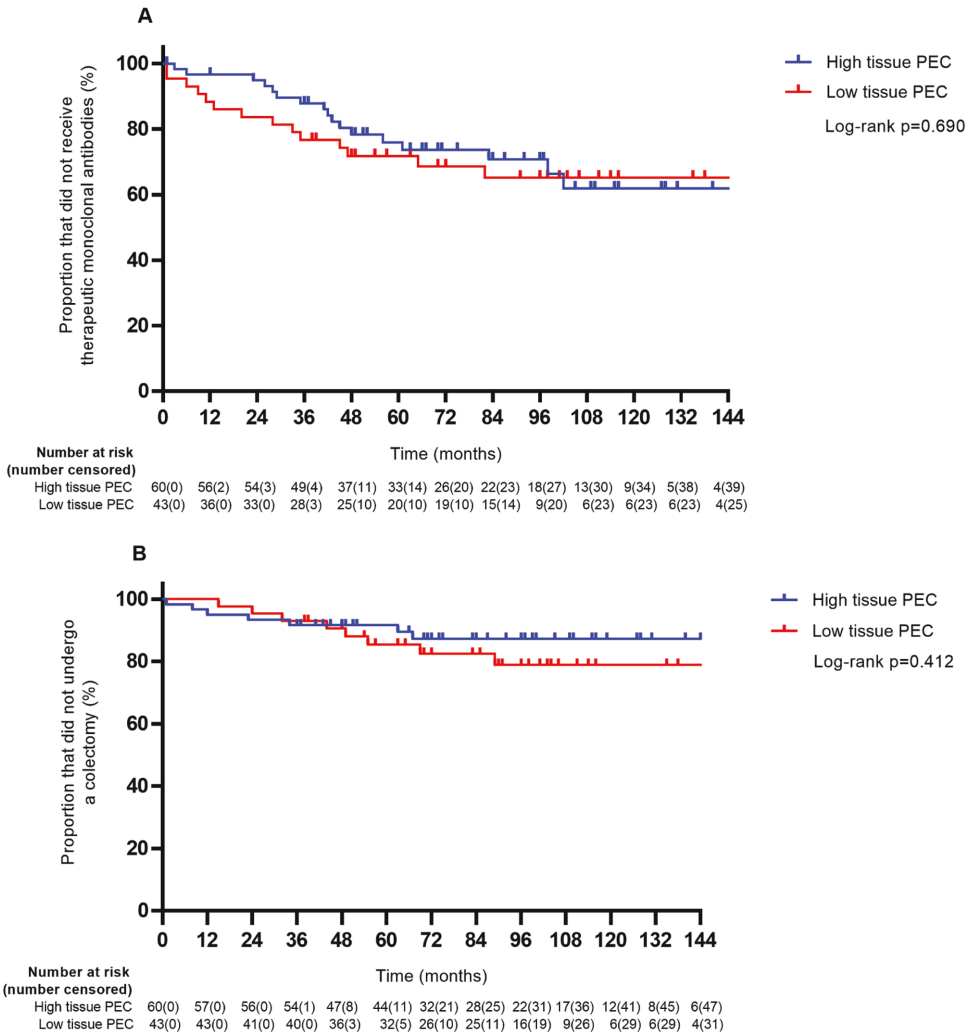

Figure 1. A and B, Time to therapeutic monoclonal antibodies and colectomy. Kaplan-Meier survival curves are shown for patients with high and low tissue peak eosinophil count (PEC). The log-rank test was used to compare the 2 groups.

low and high groups according to median cutoff point (median PEC 60) in order to perform a log-rank test (Supplementary Figure 3). A median time to event could not be calculated, as <50% of the patients ultimately received therapeutic monoclonal antibodies or underwent a colectomy, but no difference in time to initiation of therapeutic monoclonal antibodies (χ^2_1 = 0.291, P = .590) or colectomy (χ^2_1 = 0.427, P = .513) was found.

To quantify the influence of PEC on the time to initiation of therapeutic monoclonal antibodies or colectomy, univariate Cox regression analyses were performed. They showed that PEC did not influence the time to initiation of therapeutic monoclonal antibodies (HR, 0.999; 95% CI, 0.988-1.009; P = .805) or colectomy (HR, 0.988; 95% CI, 0.971-1.006; P = .203).

There was no difference in the degree of peripheral blood eosinophil count between a more severe disease course (n = 15) and a less severe disease course (n = 13) (P = .093). Peripheral blood eosinophil count was significantly higher in those patients starting with use of corticosteroids in the first year (P = .030), but no differences were found in peripheral blood eosinophil count for the other outcomes (Table 3). No correlation was found between peripheral blood eosinophil count and the number of flares in the first year (r_s = 0.261, n = 28, P = .180). Also, with a logistic regression model, peripheral blood eosinophil count could not be identified as predictor of any of the disease outcomes (Table 3). Kaplan-Meier survival analyses were conducted in order to investigate if peripheral blood eosinophil count predicts the time to initiation of therapeutic monoclonal antibodies or colectomy, after creation of low blood eosinophil count and high blood eosinophil count groups according to cutoff point 0.5 × 10^9/L in order to perform a log-rank test (Supplementary Figure 4). A median time to event could not be calculated, as <50% of the patients ultimately received therapeutic monoclonal antibodies or underwent a colectomy, but no difference in time to initiation of therapeutic monoclonal antibodies (χ^2_1 = 0.390, P = .533) or colectomy (χ^2_1 = 0.109, P = .742) was found.

To quantify the influence of peripheral blood eosinophil count on the time to initiation of therapeutic monoclonal antibodies or colectomy, univariate Cox regression analyses were performed. They showed that peripheral blood eosinophil count did not influence the time to initiation of therapeutic monoclonal antibodies (HR, 1.023; 95% CI, 0.475-2.204; P = .954) or colectomy (HR, 0.801; 95% CI, 0.181-3.535; P = .769).

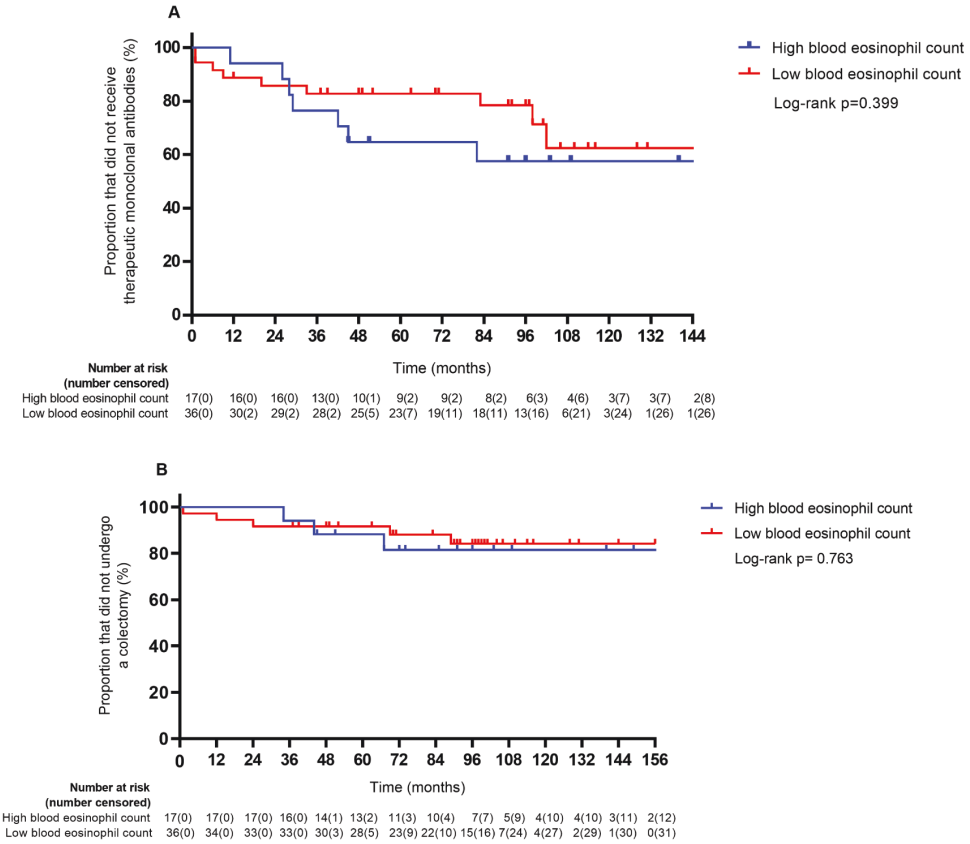

Figure 2. A and B, Time to therapeutic monoclonal antibodies and colectomy. Kaplan-Meier survival curves are shown for patients with high and low blood eosinophil count. The log-rank test was used to compare the 2 groups.

DISCUSSION

In our large cohort of newly diagnosed UC patients, baseline colonic tissue and peripheral blood eosinophil counts were not correlated with histologic and endoscopic disease activity. Moreover, baseline tissue and peripheral blood eosinophils could not be identified as short- or long-term predictors of more severe disease outcomes in UC.

This is the first cohort study to look into baseline eosinophil counts in colonic tissue and in peripheral blood of both adults and children. The associations with short- and long-term disease outcomes that represented a more severe phenotype of UC were investigated. At first, a severe phenotype of UC was defined as patients who received either corticosteroids or immunomodulators in the first year or who received therapeutic monoclonal antibodies or underwent a colectomy during entire follow-up. These outcomes were also considered separately. Neither analysis resulted in identification of tissue or blood eosinophils as predictors for these outcomes.

These data therefore do not support a relationship between the degree of tissue or peripheral blood eosinophils and histological or endoscopic disease activity. Although increased levels of tissue and peripheral blood eosinophils are widely recognized in active UC, only a few studies have investigated the correlation with clinical, endoscopic, or histological disease activity.[10,24-29] Correlations between both colonic tissue and peripheral blood eosinophils and clinical and histological disease activity (measured with UC Histologic Index of Severity) were identified in children.[8,11] In adults, Zezos et al[9] found only a correlation between colonic tissue eosinophils and histological disease activity (measured with Histological Disease Activity grading), but not with clinical or endoscopic disease activity. Other adult studies also could not demonstrate a correlation between colonic tissue eosinophils and either clinical or endoscopic disease activity.[10,30]

As a second step in this study, it was shown that baseline colonic tissue and peripheral blood eosinophilia did not have prognostic value for the disease course. The only other study that investigated baseline colonic tissue and peripheral blood eosinophils as predictors of both short- and long-term outcomes was done by Morgenstern et al.[11] In their pediatric cohort, they could not demonstrate an association with a long-term risk for step-up therapy or colectomy, which is in line with our results. However, they found an association with short-term use of corticosteroids. Despite the fact that patients who used corticosteroid treatment had significantly higher peripheral blood eosinophil count, it could not be identified as a risk factor for corticosteroid use in the first year. We can only speculate about the reasons for these differences. In our pediatric cohort, almost the same percentage of children received corticosteroids in the first year as in the cohort of Morgenstern et al; however, our cohort was smaller (34 vs 96); therefore, an association could have been missed. It is known that pediatric UC is frequently more extensive and easily progresses into more severe disease.[31] The early use of corticosteroids is not uncommon, and an association is probably more likely to be picked up than in adults. Furthermore, previous studies showed that regional differences, medication use, and also season influence the eosinophil counts both in colonic tissue and in blood.[32,33]

Most of the previous studies that suggested that eosinophils are potential markers of a more severe disease type

Table 3. The associations between PEC and peripheral blood eosinophil count and disease outcomes in children

Outcome	PEC				Peripheral Blood Eosinophil Count			
	Yes	No	*P* Value	Hazard Ratio (95%CI)	*P* Value	Yes × 10^9/L	No × 10^9/L	*P* Value	Hazard Ratio (95%CI)	*P* Value
A more severe disease course[a]	60 (55-95)	60 (40-125)	.915	0.997 (0.982-1.013)	.735	0.60 (0.24-0.89)	0.26 (0.20-0.43)	.093	1.261 (0.359-4.430)	.718
Therapeutic monoclonal antibodies during follow-up	60 (55-110)	70 (40-110)	.848	1.001 (0.986-1.016)	.939	0.58 (0.22-0.96)	0.29 (0.21-0.58)	.210	1.299 (0.385-4.382)	.673
Colectomy during follow-up	60 (45-80)	70 (45-125)	.306	0.984 (0.963-1.006)	.149	0.35 (0.18-0.95)	0.34 (0.22-0.71)	.978	0.785 (0.145-4.253)	.779
Corticosteroids treatment first year	65 (60-88)	55 (40-133)	.798	0.997 (0.982-1.012)	.655	0.70 (0.27-0.94)	0.26 (0.20-0.44)	.030	1.601 (0.424-6.035)	.487
Immunomodulator treatment first year	60 (60-80)	65 (40-155)	.717	0.988 (0.972-1.006)	.184	0.60 (0.24-0.98)	0.28 (0.20-0.56)	.120	1.409 (0.413-4.813)	.584

Values are median (interquartile range), unless otherwise indicated. Univariate logistic regression was used to analyze whether PEC or peripheral blood eosinophil count could predict the disease outcomes in children.

Abbreviations: CI, confidence interval; PEC, peak eosinophil count.

[a]A more severe disease course included patients who received either systemic corticosteroids or immunomodulators in the first year or who received therapeutic monoclonal antibodies or underwent a colectomy during entire follow-up.

are done in patients who already received different forms of therapy.[9,13] We know from several case reports that mesalazine can induce eosinophilia.[34,35] Many patients with UC are on these types of drugs, as it is a first-line treatment option.[1] Contrasting data also exist. In 2 studies, a lack of eosinophils in biopsies during follow-up was associated with more severe disease ultimately requiring surgery.[15,16] Many of the patients that ultimately required surgery were on high doses of corticosteroids for a longer period of time, which has a profound effect on eosinophilic infiltration.[36] This could explain the lack of eosinophils in these patients. It is possible that the role of eosinophils in UC is overestimated because of the influence of different treatments on the eosinophil counts. Moreover, it is unclear what the effect of disease duration is on the eosinophil count.

This is the first study to investigate the predictive value of colonic and peripheral blood eosinophils in a large cohort consisting of both adults and children using data collected at diagnosis. We applied strict inclusion and exclusion criteria to make sure that there was no other logical explanation for the blood and tissue eosinophilia. Concomitant medications were screened for possible effects on colonic and peripheral blood eosinophils. Another strength is the evaluation of the biopsies by a single experienced pathologist who was blinded from the disease outcomes.

However, we acknowledge several limitations. First, this study is restricted by the retrospective nature of the study. Because of incomplete clinical information, we could not investigate the relation of tissue and peripheral blood eosinophils with clinical disease activity. In about 25% of the patients, no detailed description of the biopsy site was available. Microscopic heterogeneity could be a possible confounder in this study, as it is a retrospective study, and therefore no standard biopsy protocol was used.[21]Despite the limitations, we do not believe that these have any significant influence on the study results. The data were carefully screened for bias and presence of cofounders.

CONCLUSIONS

This large cohort study in both adults and children with UC shows that baseline tissue or peripheral blood eosinophils are not a marker of disease activity and cannot be used as a predictor of severe disease outcomes in UC.

Supplementary data

Supplementary data is available at *Inflammatory Bowel Diseases* online.

Acknowledgments

None.

Supported By

None to declare.

Conflicts of Interest

M.L.H. has none to declare. A.M. has received speaker fees from Roche and Pfizer. M.D. has served as advisor for Echo Pharmaceuticals B.V. and Robarts Clinical Trials; received

speaker fees from Janssen, Merck, Pfizer, Takeda, and Tillotts Pharma; and received nonfinancial support from Dr. Falk Pharma. G.R.A.M.D.H. has served as advisor for AbbVie, Ablynx, Amakem, AM Pharma, Avaxia, Biogen, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmo, Covidien, Ferring, Dr. Falk Pharma, Engene, Galapagos, Gilead, GlaxoSmithKline, Hospira, Immunic, Johnson and Johnson, Lycera, Medimetrics, Millennium/Takeda, Mitsubishi Pharma, Merck Sharp Dome, Mundipharma, Novonordisk, Pfizer, Prometheus Laboratories/Nestlé, Protagonist, Receptos, Robarts Clinical Trials, Salix, Sandoz, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant, and Vifor; and received speaker fees from AbbVie, Ferring, Johnson and Johnson, Merck Sharp & Dohme, Mundipharma, Norgine, Pfizer, Shire, Millennium/Takeda, Tillotts, and Vifor. A.J.B. has received research funding from Nutricia, Norgine, Thelial, SST, and Bayer; and speaker and/or consulting fees from Alimentiv, Laborie, EsoCap, Medtronic, Dr. Falk Pharma, Calypso Biotech, Reckitt Benckiser, Regeneron, and AstraZeneca.

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