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Blood eosinophilia in patients with inflammatory bowel disease losing response to biologics

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Abstract

Background Emerging data suggest that blood eosinophilia may be linked to inflammatory bowel disease (IBD) activity and biologic treatment failure. This study assessed the occurrence of eosinophilia in IBD patients experiencing biologic failure.

Methods This was a single-center retrospective study of IBD patients treated with infliximab (IFX) or vedolizumab (VDZ) between 2017 and 2023. Demographics, disease characteristics, disease activity, treatment modifications, together with data on blood eosinophilia and persistent blood eosinophilia, were recorded at 1-year follow up following treatment initiation with biologics. The outcomes were rate of biologic failure, hospitalizations, and surgery at 1 year. Uni- and multivariate analyses were performed to identify factors associated with these outcomes.

Results The study included 154 patients, 96 with Crohn's disease (CD) (62.3%) and 58 with ulcerative colitis (UC) (37.7%). The occurrence of blood eosinophilia was observed in 22% of patients over 1 year of follow-up. In univariate analysis, factors associated with biologic failure included previous biologic exposure (P<0.001), baseline immunosuppressants (P=0.009), baseline perinuclear antineutrophil cytoplasmic antibody (P=0.041), and blood eosinophilia (P=0.037). Blood eosinophilia was associated with a higher risk of VDZ failure (odds ratio [OR] 2.81, 95% confidence interval [CI] 1.01-8.10; P=0.047) and was more frequently observed in patients with CD than in UC (OR 2.97, 95%CI 1.05-8.91; P=0.040). Multivariate analysis confirmed the association of blood eosinophilia and biologic failure (OR 2.65, 95%CI 1.08-6.65; P=0.034).

Conclusion Blood eosinophilia was independently associated with biologic failure at 1 year in IBD patients and may represent a risk-stratifying biomarker.

Keywords Blood eosinophilia, inflammatory bowel disease, ulcerative colitis, Crohn's disease, biologics

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Introduction

Biologic therapies have revolutionized the management of inflammatory bowel disease (IBD), including ulcerative colitis (UC) and Crohn's disease (CD) [1]. However, despite an initial response in over two thirds of patients, a substantial proportion will ultimately experience a secondary loss of response (LOR) over time [2,3]. These secondary non-responders—unlike primary non-responders, who fail to achieve clinical benefit within the first 14 weeks of treatment [4]—pose a major clinical challenge in daily practice. The unpredictability of LOR complicates therapeutic decisions, especially in the absence of a comprehensive understanding of its underlying mechanisms [5].

While known factors such as a high inflammatory burden (leading to increased mucosal drug clearance and drug scavenging) and immunogenicity (e.g., development of neutralizing antibodies) account for a significant part of LOR [6], other mechanisms have been proposed but remain largely uncharacterized. These mechanisms include enhanced drug catabolism, potentially via the reticuloendothelial system, and a phenomenon referred to as immune shift [7]. Elucidating these mechanisms is a critical unmet

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need, as identifying surrogate biomarkers could enable earlier detection of biologic failure and guide more effective therapeutic strategies [2].

Eosinophils, classically implicated in allergic conditions such as asthma, atopic dermatitis, and eosinophilic gastroenteritis, have also emerged as key players in Th2-mediated inflammation, in several inflammatory disorders such as IBD [8]. During early intestinal inflammation, a Th2 immune response predominates before transitioning into a more chronic Th1 profile [9]. Under interleukin (IL)-5 stimulation, eosinophils differentiate in the bone marrow, enter the bloodstream, and home to the inflamed gut mucosa, where they release cytotoxic granules (eosinophil cationic protein, eosinophil peroxidase, eosinophil-derived neurotoxin, and major basic protein) thereby exacerbating inflammation and tissue damage [10-12]. Indeed, eosinophilic infiltration and elevated granule protein levels have been correlated with disease activity [13]. Moreover, blood eosinophilia has been reported in up to 20% of IBD patients [14], and appears to be linked to a more severe disease course and biologic failure [15-17]. These findings highlight the potential role of eosinophils, not only as effector cells, but also as risk-stratifying biomarkers of IBD biologic failure [18].

In this context, our study aimed to examine the relationship between blood eosinophilia and LOR to infliximab (IFX) and vedolizumab (VDZ) in IBD patients, addressing a clinically relevant gap and advancing the search for risk-stratifying biomarkers of therapeutic failure.

Patients and methods

Study design

We conducted a retrospective single-center study by reviewing the medical records of IBD patients treated with infliximab (IFX) or vedolizumab (VDZ) between January 2017 and December 2022 at Erasme Hospital. All data were collected with the approval of the Erasme Hospital ethics committee, obtained on November 23, 2023 (Ref: P2023-302).

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Inclusion/exclusion criteria

The inclusion criteria were being diagnosed with IBD (CD or UC), age >18 years, regular follow-up for IBD (follow up of 52 weeks on treatment, unless the medication was prematurely discontinued due to primary non-response) at Erasme hospital, and treatment with IFX or VDZ. The exclusion criteria were being treated with a therapy other than VDZ or IFX, or having incomplete medical records.

Study population

In total, 374 patients received biologic treatments, whereas 220 patients were excluded from the initial cohort for the following reasons: 38 patients were part of both the VDZ and IFX cohorts, 27 patients received only a single dose of biologics between 2017 and 2023, 14 had incomplete medical records, 42 had a treatment duration of less than 16 weeks for other reason than primary non-response, 99 (96 IFX, 3 VDZ) were excluded after propensity score matching (phenotypic matching based on the disease duration, presence of asthma or allergies, and corticosteroid exposure.). Finally, 154 patients were included in downstream analyses, 77 treated with IFX and 77 treated with VDZ (Fig. 1A).

Data collection

Clinical, biological, and endoscopic data were collected using the medical record, allowing for a chronological follow up of events.

At baseline (start of biologic treatment)

Phenotypic data (sex, body mass index, year of birth, date of IBD diagnosis, medical history, surgical history), treatment history (IFX or VDZ, concomitant IBD treatments), patient-reported outcome (PRO-2) clinical score, as well as the following biological data: C-reactive protein (CRP), fecal calprotectin (FC), blood eosinophil levels, immunoglobulin E, antinuclear antibody (ANA), perinuclear antineutrophil cytoplasmic antibody (pANCA), complete blood count (CBC), imaging data, presence of eosinophils in intestinal biopsies, stool parasitological examination.

At the end of biologic induction (between weeks 8-14), at weeks 16-32, and at 1 year (weeks 48-52)

Clinical evaluation (PRO-2 clinical score), biological data (CRP, FC, blood eosinophil levels, CBC), imaging procedures and presence of eosinophils in biopsies performed during follow-up endoscopy. We also collected IBD-related hospitalization and surgery rates at 1 year.

For CD patients, clinical remission was defined using PRO-2: mean daily abdominal pain score ≤1 and mean

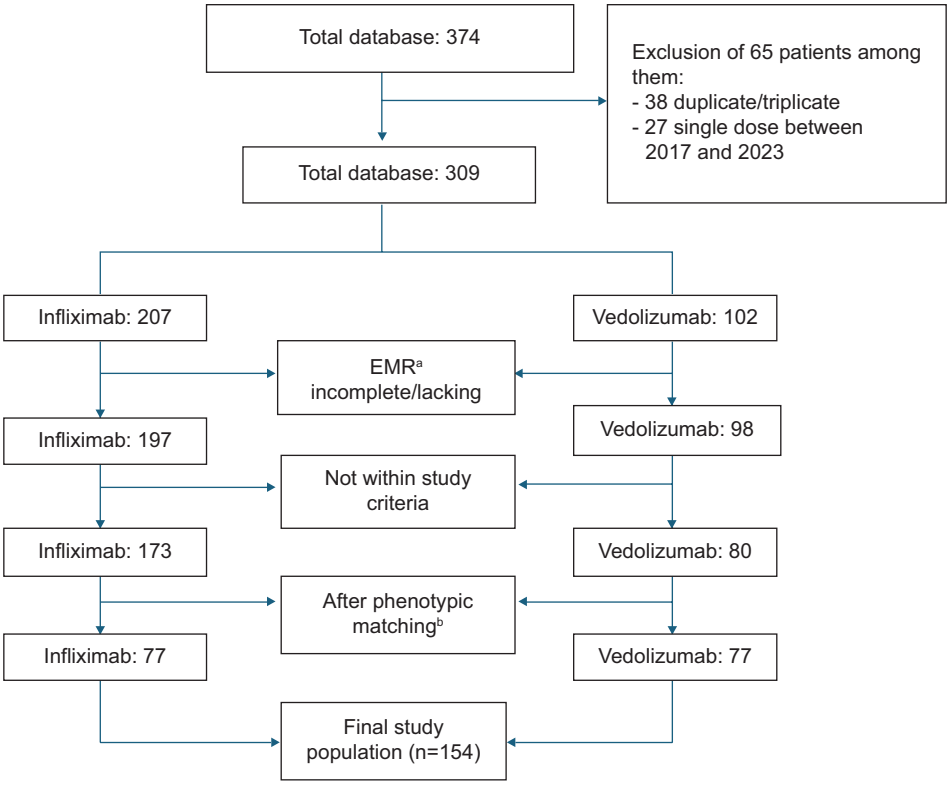

Figure 1 (A) Flowchart of the overall population
[a]EMR, Electronic medical record
[b]Phenotypic matching based on propensity score matching (disease duration, presence of asthma or allergies and corticosteroids exposure)

Disease activity	Endoscopic scores for CD (SES-CD)	Endoscopic scores for UC (Mayo)
Quiescent	SES-CD ≤ 3	Endoscopic Mayo score 0
Mildly active	4 ≤ SES-CD ≤ 10	Endoscopic Mayo score 1
Moderately active	11 ≤ SES-CD ≤ 20	Endoscopic Mayo score 2
Severely active	SES-CD > 20	Endoscopic Mayo score 3

Figure 1B The Mayo and SES-CD score
CD, Crohn's disease; UC, ulcerative colitis; SES-CD, Simple Endoscopic Score for Crohn's disease

daily stool frequency score ≤3. For UC patients, remission was defined as mean daily stool frequency ≤1 and rectal bleeding =0. Conversely, clinical worsening was defined as a worsening of the PRO-2 score over time, reflected by an increase of ≥1 point in either subscore or a ≥50% increase in the total PRO-2 score.

The Mayo score and the Simple Endoscopic Score for Crohn's disease (SES-CD) were used to score endoscopic activity for UC and CD patients, respectively (Fig. 1B).

For CD, endoscopic response was defined as a ≥50% decrease in the SES-CD score; for UC, it was defined as a decrease of ≥1 point in the Mayo endoscopic subscore.

We defined worsening or absence of endoscopic response as a lack of improvement in the endoscopic score (SES-CD or Mayo) between baseline and the follow-up endoscopy performed between 6 and 12 months after initiation of biologic treatment.

We defined patients with blood eosinophilia as those with absolute eosinophil counts ≥0.5 × 10^9/L. In addition, tissue eosinophils were identified in the histopathology report of the biopsies at baseline and after 1 year of treatment on follow up endoscopy, assessed as a binary value (presence/absence).

The patient population was stratified into 2 categories: (1) patients with blood eosinophilia at least once during follow up; (2) patients with blood eosinophilia at ≥2 time points during the study (classed as persistent blood eosinophilia), thereby excluding patients with eosinophilia observed at a single time point only.

We also managed to investigate patients with tissue eosinophilia, and patients with both tissue and blood eosinophilia. Tissue eosinophilia was considered as a binary variable, given the absence of quantitative eosinophil counts in routine histopathological reports. Consequently, a precise assessment of tissue eosinophil density was not feasible in this retrospective context.

Definition and outcomes

The primary outcome was to evaluate whether blood eosinophilia was associated with biological failure. In this

study, biologic failure was defined as treatment interruption for loss of clinical response and/or endoscopic worsening during the follow-up period. Secondary outcomes were to evaluate whether blood eosinophilia was associated with the rate of hospitalization and surgery related to IBD during the follow-up period.

Covariates

Patients were defined as non-allergic if they had no reported history of allergy. Use of corticoids was considered at each time point (baseline, weeks 8-14, weeks 16-32, and weeks 48-52) and was divided into 2 categories: topical corticoids, such as budesonide or beclomethasone, or systemic corticoids, such as methylprednisolone.

Statistical analysis

Summary statistics was performed on the normal distribution of all quantitative data was evaluated using graphics. Continuous variables were presented using medians and interquartile ranges, then compared using Student's *t*- or Mann-Whitney *U* tests, as appropriate. Proportions were used to express categorical variables, which were analyzed using χ^2 tests or Fisher's exact tests, as appropriate. Propensity score matching (see study population) was used to ensure the most appropriate comparison of patients treated with IFX or VDZ. This matching was based on the disease duration and known eosinophilia-related confounding factors, such as the presence of asthma, allergies and systemic corticosteroid exposure. Univariate logistic regression was conducted within the overall population to estimate the association between collected variables and the 3 outcomes. The same analysis was performed again in the 2 sub-cohorts (IFX and VDZ). The significance threshold was set at 0.05. Variables that were statistically significant in univariate analysis were entered into a multivariable model using forward selection. The analyses were conducted using R and Jamovi software.

Results

Study cohort

A total of 154 IBD patients were included in the study, of whom 96 (62.3%) had CD and 58 (37.7%) had UC. Table 1 and Supplementary Table 1 show the patient characteristics of the 2 biologic cohorts. Importantly, the number of UC patients in the VDZ cohort (52%) was significantly higher compared to the IFX cohort (23%) (P<0.001). Consequently, differences arose in variables in the 2 sub-cohorts, such as the use of an immunomodulator (P=0.009) or Janus kinase inhibitor (P=0.010), the presence of ANA/pANCA positivity (P=0.015, P<0.001), prior IBD surgery (P=0.030) or anal surgery (P=0.003), as well as the type of corticoids (topical vs. systemic) (P=0.002). However, the use of propensity score matching allowed us to achieve comparable proportions between CD and UC sub-cohorts for some important covariates, such as asthma, allergy and systemic corticosteroid exposure.

Eighty-two patients (53%) were on corticoids at baseline, indicating a very severe population usually seen in a tertiary care center.

Table 1A Methotrexate or azathioprine or 6-mercaptopurine; bJanus kinase inhibitor tofacitinib or upadacitinib

Parameter	All patients (n=154)	Infliximab group (n=77)	Vedolizumab group (n=77)	P-value
Disease features (n, %)				<0.001
Ulcerative colitis	58 (37.7)	18 (23.4)	40 (51.9)	
Crohn's disease	96 (62.3)	59 (76.6)	37 (48.1)	
Asthma (n, %)	8 (5.2)	4 (5.2)	4 (5.2)	>0.99
Allergy (n, %)	41 (26.6)	23 (29.9)	18 (23.4)	0.362
Number of biologics (n, %)				0.012
1	64 (41.6)	38 (49.4)	26 (33.8)	
2	39 (25.3)	13 (16.9)	26 (33.8)	
3	25 (16.2)	9 (12.5)	16 (20.8)	
>3	26 (16.9)	17 (22.1)	9 (11.7)	
Concomitant medication (n, %)				
Immunomodulator[a]				0.009
None	55 (35.9)	20 (26)	35 (46.1)	
1	91 (59.5)	55 (71.4)	36 (47.4)	0.010
2	7 (4.6)	2 (2.6)	5 (6.6)	
JAKi[b]				
None	145 (94.8)	69 (86.6)	77 (100)	
1	7 (4.6)	7 (9.1)	0	
2	1 (0.7)	1 (1.3)	0	

[a]Methotrexate of azathioprine of 6-mercaptopurine; [b]Jason kinase inhibitor tofacitinib or upadacitinib

Table 1B Baseline data of the study population

Parameter	All patients (n=154)	Infliximab group (n=77)	Vedolizumab group (n=77)	P-value
Endoscopy at baseline[a]				
CD (SES-CD) (n, %)				0.195
No activity (<4)	26 (26)	16 (28.1)	10 (23.3)	
Mild to moderate activity (4-20)	61 (61)	31 (54.4)	30 (69.8)	
Severe activity (>20)	13 (13)	10 (17.5)	3 (7.0)	
UC (Mayo subscore) (n, %)				0.167
No activity (0)	5 (10.4)	1 (3.3)	4 (22.2)	
Mild activity (1)	6 (12.5)	4 (13.3)	2 (11.1)	
Moderate to severe activity (2-3)	37 (77.1)	25 (88.3)	12 (66.7)	
Clinical PRO at baseline				
CD(PRO2) (n, %)				0.112
0	13 (12.7)	5 (8.8)	8 (17.8)	
1	30 (29.4)	14 (24.6)	16 (35.6)	
2	59 (57.8)	38 (66.7)	21 (46.7)	
UC(PRO2) (n, %)				0.510
0	9 (17.6)	2 (10.5)	7 (21.9)	
1	10 (19.6)	3 (15.8)	7 (21.9)	
2	32 (62.7)	14 (73.7)	18 (56.2)	
Corticosteroids baseline (n, %)				
Yes	82 (53.2)	41 (53.2)	41 (53.2)	>0.99
No	72 (46.8)	36 (46.8)	36 (46.8)	
Type of corticosteroids (n, %)				
Topical	27 (32.5)	7 (16.7)	20 (48.8)	0.002
Systemic	56 (67.5)	35 (83.3)	21 (51.2)	
Positive serology, N (n, [%])				
ANA	148 (39 [26.4])	74 (13 [17.6])	74 (26 [35.1])	0.015
pANCA	127 (40 [31.5])	70 (11 [15.7])	57 (29 [50.9])	<0.001
IgE	20 (11 [7.1])	12 (5 [6.5])	9 (6 [7.8])	0.754
Stools analysis baseline				
FC (median, IQR 25-75)[b]	500 (164-2379)	492 (179-2263)	547 (160-2324)	0.937
Fecal parasitosis (n, %)[c]	3 (2.3)	1 (1.5)	2 (3.1)	0.614
Yes[d]				

[a]Endoscopy baseline missing data: 6 patients total, 2 IFX, 4 VDZ
[b]Missing fecal calprotectin data: 58 patients total, 39 IFX, 19 VDZ
[c]Missing fecal parasitosis data: 23 patients total, 10 IFX, 13 VDZ
[d]Only Blastocytis hominis
CD, Crohn's disease; UC, ulcerative colitis; SES-CD, Simple Endoscopic Score for Crohn's disease; PRO, patient-reported outcome; ANA, antinuclear antibody; pANCA, perinuclear antineutrophil cytoplasmic antibody; IQR, interquartile range; FC, fecal calprotectin; IFX, infliximab; VDZ, vedolizumab

Prevalence of eosinophilia in the study cohort

Overall, a total of 34 patients, representing 22% of the overall population, were categorized as having blood eosinophilia. Thirteen of these patients were treated with IFX and 21 with VDZ (Table 2). There was no significant difference in the distribution of IBD subtypes (UC 16 [27.6%] and CD 18 [18.8%], P=0.200) (Supplementary Table 2).

On a longitudinal view, 16 patients at baseline, 17 at 8-14 weeks, 9 at 16-32 weeks and 15 at 48-52 weeks were classified as having blood eosinophilia (Fig. 2). Regarding blood eosinophilia patterns, single-time blood eosinophilia was observed in 9.8% of responders and 16.1% of patients with biologic failure. Persistent blood eosinophilia at 2 time points was comparable between groups (4.3% vs. 4.8%), while persistent blood eosinophilia across 3 time points was more frequent in patients with biologic failure (9.7% vs. 0%) (Supplementary Table 3). In parallel, a longitudinal overview of corticosteroid tapering is provided in Supplementary Table 4.

Regarding intestinal biopsies, 43 (33.6%) patients had tissue eosinophilia. Nineteen of these patients were treated with IFX and 24 with VDZ (Table 2). In this cohort, 8 patients had tissue eosinophilia in the upper gastrointestinal (GI) tract and 35 in the lower GI tract, with no significant difference between the IFX and VDZ cohorts (17.2% lower GI tract UC and 10.2% lower GI tract CD, P=0.147). In addition, 29 patients presented tissue eosinophilia at baseline and 25 at the end of follow up. Among these, both blood and tissue eosinophilia were observed in 15 patients.

Eosinophils in biologic failure

We investigated variables potentially associated with biologic failure (Table 3). In univariate analysis, prior exposures

Table 2 Prevalence of eosinophilia (>500/mm^3)

Parameter	All patients (n=154)	Infliximab group (n =77)	Vedolizumab group (n=77)	P-value
Eosinophilia (n, %)				
Blood eosinophilia (> 500/mm^3)	34 (22.1)	13 (16.9)	21 (27.3)	0.120
Tissue eosinophilia (yes vs no)	43 (33.6)	19 (31.7)	24 (35.3)	0.665
Persistent eosinophilia (> 2 timepoints)	15 (9.7)	7 (9.1)	8 (10.4)	0.786
Eosinophilia during time[a] (n, %)				
At baseline	16 (10.6)	6 (7.8)	10 (13.5)	0.25
At 8-14 weeks	17 (12.9)	9 (12.7)	8 (13.1)	0.94
At 16-32 weeks	9 (7.3)	1 (1.5)	8 (14.0)	0.012
At 48-52 weeks	15 (13.4)	6 (10.2)	9 (17.0)	0.41

[a]Blood eosinophilia missing data: 3 baseline, 22 8-14 weeks, 31 16-32 weeks, 42 48-52 weeks
UC, ulcerative colitis; CD, Crohn's disease

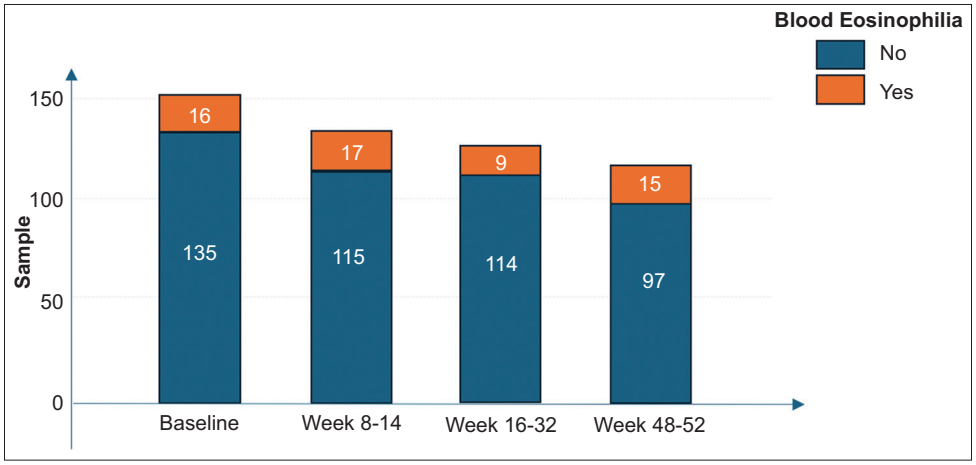

Figure 2 Prevalence of blood eosinophilia. This histogram illustrates the change in eosinophil count over different timepoints for patients undergoing treatment by biologics. The x-axis represents time intervals (weeks), while the y-axis represents the sample. Each bar represents the sample of blood eosinophilia for a specific time interval, with orange bars indicating the presence of blood eosinophilia. The decrease in sample size over time is linked both to treatment cessation and to missing data

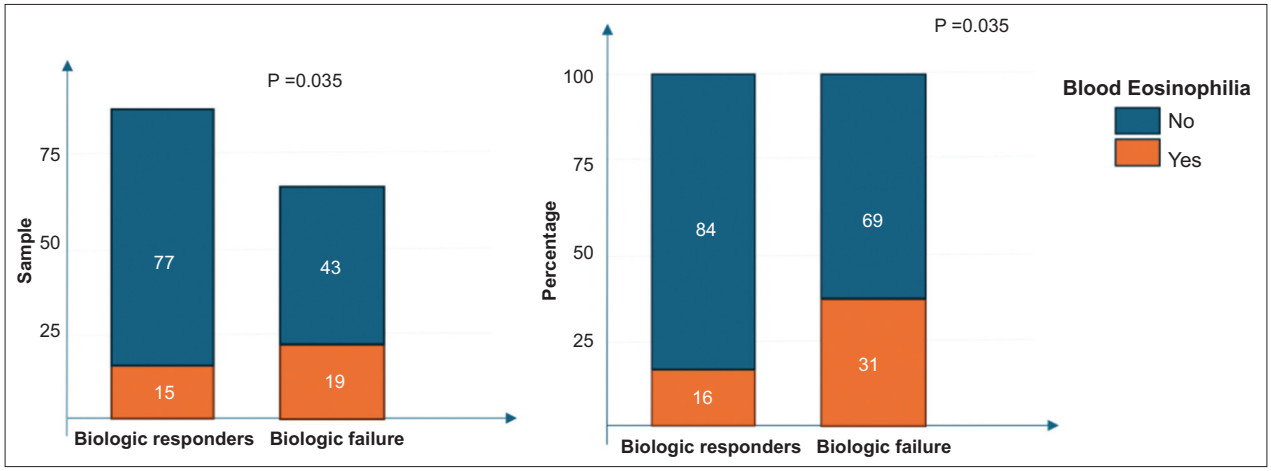

Figure 3 Blood eosinophilia and biologic failure. The presence of blood eosinophils was associated with biologic failure (χ^2 test P-value 0.035). Thirty-one percent of patients with blood eosinophils experienced biologic failure compared to 16% of biologic responders

to biologics, immunosuppressant use at baseline, and the presence of pANCA were all associated with biologic failure. Moreover, blood eosinophilia was associated with biologic failure (odds ratio [OR] 2.27, 95% confidence interval [CI] 1.05-

Table 3 Logistic regression models for biologic failure

Variable	Univariate analysis			Multivariate analysis		
	OR	95%CI	P	OR	95%CI	P-value
FC baseline	1.00	1.00, 1.00	0.16			
Smoking status (yes vs. no)	0.68	0.28, 1.56	0.37			
Prior surgery (yes vs. no)	1.69	0.85, 3.35	0.13			
Type IBD (UC vs. CD)	0.93	0.48, 1.81	0.83			
Associated IMID (yes vs. no)	1.24	0.54, 2.79	0.60			
Allergy baseline (yes vs. no)	1.23	0.59, 2.53	0.58			
Prior biologic exposure	2.52	1.83, 3.62	<0.001	2.60	1.86, 3.79	<0.001
IMM baseline	2.49	1.26, 4.97	0.008			
Corticoids baseline	1.24	0.65, 2.38	0.51			
CRP Baseline	1.00	0.98, 1.01	0.94			
pANCA baseline (positive/negative)	2.21	1.03, 4.79	0.041			
Blood eosinophilia baseline	3.87	0.70, 22.7	0.12			
Blood eosinophilia wk 8-14	2.44	0.43, 14.6	0.31			
Blood eosinophilia wk 16-32	1.90	0.20, 18.0	0.57			
Blood eosinophilia wk 48-52	14.9	1.90, 137	0.010			
Blood eosinophilia (yes/no)	2.27	1.05, 4.98	0.037	2.65	1.08, 6.65	0.034
Persistent BE (yes/no)	2.43	0.83, 7.63	0.10			
Tissue eosinophilia (yes/no)	1.90	0.91, 4.04	0.088			

OR, odds ratio; CI, confidence interval; IMM, immunomodulator; BMI, body mass index; ANA, antinuclear antibody; pANCA, perinuclear antineutrophil cytoplasmic antibody; BE, blood eosinophilia

4.98; P=0.037), with a higher prevalence among patients with biologic failure compared to responders (31% vs 16%, P=0.035; Fig. 3). In multivariate analysis, both blood eosinophilia and prior exposures to biologics remained significantly associated with biologic failure, with ORs of 2.65 (95%CI 1.08-6.65; P=0.034) and 2.60 (95%CI 1.86-3.79; P<0.001), respectively.

Fourteen patients required surgery related to IBD, of whom 5 had blood eosinophilia (35%). In univariate analysis (Supplementary Table 5), there was no significant link between blood eosinophilia and surgery. Likewise, no significant association was demonstrated between eosinophils (blood and tissue) and the rate of hospitalization during the follow up.

Is blood eosinophilia associated with the class of biologic therapy?

Given the results mentioned above, it is worth considering whether blood eosinophilia is associated with treatment failure specific to a particular biologic agent (VDZ or IFX), or whether it represents a general associative marker of biologic failure, regardless of the biologic used. In univariate analysis (Supplementary Table 6), the presence of blood eosinophilia was associated with a greater risk of VDZ failure (OR 2.81, 95%CI 1.01-8.10; P=0.047). In contrast, no significant association was found between blood eosinophilia and treatment failure in the IFX cohort (OR 1.82, 95%CI 0.54-6.26; P=0.330).

Is blood eosinophilia associated with the IBD subtype?

Since VDZ was more frequently administered to UC patient in our cohort, the observed association between blood eosinophilia and VDZ raises the possibility that this relationship may reflect differences between IBD subtypes, rather than a specifically biologic effect. In UC patients, blood eosinophilia (OR 1.63, 95%CI 0.50-5.28; P=0.410) did not constitute a risk factor for biologic failure (Supplementary Table 7). However, in CD patients, the presence of blood eosinophilia was associated with a higher risk of biologic failure (OR 2.97, 95%CI 1.05-8.91; P=0.040).

Discussion

This study evaluated the relationship between peripheral blood eosinophilia and biologic treatment failure in a biologic-matched cohort of patients with IBD receiving IFX or VDZ. In this retrospective cohort, blood eosinophilia emerged as an independent risk factor for biologic failure at 1 year. This association was particularly strong in patients with CD and in those treated with VDZ.

Peripheral eosinophilia has previously been associated with a more aggressive IBD phenotype, increased healthcare

utilization and a higher inflammatory burden [15,16,19]. In line with these observations, we confirmed that peripheral blood eosinophilia may serve as a risk-stratifying biomarker for IBD patients, with higher eosinophil levels observed among those who subsequently experienced biologic failure during 1 year of follow up. In addition, although our results do not establish causality, they support the potential value of eosinophil monitoring as a part of longitudinal assessment.

Beyond the observed relationship between blood eosinophilia and IBD severity (reflected by failure of biologic therapy), we specifically examined the association between blood eosinophilia and treatment failure with 2 biologic agents, IFX and VDZ, in a biologic-matched cohort of IBD patients. To our knowledge, this is the first study specifically designed to address this question. In the literature, data regarding the association between eosinophilia and anti-tumor necrosis factor (TNF) therapies have been heterogeneous. Some studies [20,21] have reported that blood eosinophilia before starting anti-TNF therapy predicts poorer outcomes and earlier anti-TNF discontinuation, particularly in CD. More specifically, our team conducted a multicenter prospective study that suggested a potential role for eosinophilia in predicting patients' response to IFX [22]. In contrast, other cohorts did not observe a clear association between blood eosinophilia and IFX failure [23]. In this context of conflicting literature, we did not observe a significant association within the IFX subgroup in the presented study. These discrepancies may relate to differences in the timing of eosinophil assessment (baseline versus longitudinal), study design, and adjustment strategies. Regarding VDZ, mucosal eosinophilia has been reported as a potential predictor of reduced therapeutic efficacy [13]. In our study, blood eosinophilia was associated with VDZ failure in univariate analysis. However, this relationship did not remain significant in multivariate analysis and therefore should be interpreted with caution. Mechanistically, the association between eosinophilia and biologic failure raises the hypothesis that a subset of IBD patients may exhibit a distinct inflammatory profile. One possible explanation could involve a relative predominance of Th2-driven or immune-allergic pathways. Eosinophils are key effector cells in Th2 immunity and have been implicated in mucosal inflammation and tissue damage in IBD [8]. However, our study was not designed to address this hypothesis, which remains speculative at this stage. To delve deeper, if confirmed in prospective studies, this immunological framework could have therapeutic implications. Targeted therapies modulating eosinophil pathways, such as anti-IL-5 agents including mepolizumab, have demonstrated efficacy in eosinophilic disorders and are being explored in inflammatory conditions [24,25]. For now, extrapolation to IBD remains premature, and further translational research is needed to determine whether eosinophilia identifies a biologically distinct subgroup amenable to such strategies.

Several limitations must be mentioned. First, multiple factors are known to affect peripheral eosinophil counts. Corticosteroid therapy, a cornerstone in the management of hypereosinophilia [26], reduces both circulating eosinophil levels and related tissue damage [27]. Although corticosteroid use was included in our propensity score matching and multivariable analyses, and was not associated with biologic failure, differences in baseline topical corticosteroid use persisted between biologic subgroups. In addition, a residual imbalance in IBD subtype distribution remained after matching, with an overrepresentation of UC in the VDZ cohort, reflecting real-world prescribing patterns. Second, the retrospective design and the presence of missing data may limit the interpretations and generalizability of our results. Third, tissue eosinophilia was recorded as a binary variable, as the non-quantitative pathology reporting limited histological precision. Future studies incorporating quantitative histological assessment would strengthen the interpretation of these findings. Fourth, follow-up was limited to 1 year, and the occurrence of eosinophilia beyond this timeframe cannot be excluded. Finally, the propensity score matching was applied to reduce imbalance in eosinophilia confounders among IFX and VDZ cohorts, but this approach resulted in a reduced sample size, which may have limited the study's statistical power. In addition, residual confounding cannot be excluded despite this matching, and the exclusion of unmatched patients may have introduced selection bias.

On the other hand, the study has notable strengths. These include objective criteria for biologic failure (integrating both endoscopic worsening and treatment discontinuation for loss of response), and adjustment for key confounders known to influence peripheral eosinophil levels. By integrating longitudinal clinical and biological data, this study offers novel insight into the potential role of eosinophilia in shaping treatment response dynamics.

In conclusion, blood eosinophilia was independently associated with biologic failure in IBD patients at 1 year of follow up. It suggests that peripheral blood eosinophil monitoring may help identify patients at increased risk of treatment failure and warrants prospective validation and mechanistic investigation.

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Statement of Ethics

All data were collected with the approval of the Erasme Hospital ethics committee, obtained on 23/11/2023 (Ref: P2023-302).

Summary Box

What is already known:

- Biologic therapies are effective in inflammatory bowel disease (IBD), but a substantial proportion of patients develop a secondary loss of response over time
- Reliable biomarkers associated with loss of response to biologic therapy remain limited
- Peripheral blood eosinophilia has been described in up to 20% of IBD patients, and has been associated with greater disease activity and a more severe clinical course; however, the literature is conflicting

What the new findings are:

- In a biologic-matched IBD cohort treated with infliximab or vedolizumab, peripheral blood eosinophilia was independently associated with biologic failure at 1 year
- In biologic-specific analyses, blood eosinophilia was associated with vedolizumab failure in univariate analysis

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Supplementary material

Supplementary Table 1 Additional demographic data of the study population

Parameter	All patients (n=154)	Infliximab group (n=77)	Vedolizumab group (n=77)	P-value
Crohn's disease				
Age at diagnosis (n, %)				0.057
A1	19 (18.6)	11 (25)	8 (13.8)	
A2	60 (58.8)	20 (45.5)	40 (69.0)	
A3	23 (22.5)	13 (29.5)	10 (17.2)	
Location (n, %)				0.552
L1	33 (32.4)	16 (36.4)	17 (29.3)	
L2	14 (13.7)	6 (13.6)	8 (13.8)	
L3	33 (32.4)	11 (25.0)	22 (18.76)	
+L4	22 (21.6)	11 (25.0)	11 (12.51)	
Behavior (n, %)				0.897
B1	55 (53.9)	23 (52.3)	32 (55.2)	
B2	21 (20.6)	10 (22.7)	11 (19.0)	
B3	26 (25.5)	11 (25)	15 (25.9)	
Anoperineal disease	19 (15.7)	6 (13.6)	13 (16.9)	0.637
Ulcerative colitis (n, %)				
Extent				0.187
E1	5 (9.4)	2 (5.7)	3 (16.7)	
E2	26 (49.1)	20 (57.1)	6 (33.3)	
E3	22 (41.5)	13 (37.1)	9 (50.0)	
Smoking status (n, %)				0.095
Not or previous	111 (78.7)	56 (84.8)	55 (73.3)	
Yes	30 (21.3)	10 (15.2)	20 (26.7)	
Prior surgery (n, %)				0.03
No	102 (66.7)	57 (75)	45 (58.4)	
Yes	51 (33.3)	19 (25)	32 (41.6)	
Anal surgery (n, %)				0.003
No	106 (86.2)	71 (93.4)	35 (74.4)	
Yes	17 (13.8)	5 (6.6)	12 (25.5)	
Comorbidity (n, %)				0.569
Associated IMID[a]	118 (79.7)	58 (81.7)	60 (77.9)	
No	30 (20.3)	13 (18.3)	17 (22.1)	
Yes				

[a]Primary sclerosing cholangitis, rheumatoid arthritis, ankylosing spondylitis, auto-immune hepatitis, uveitis, systemic lupus erythematosus, psoriasis, Hidradenitis suppurativa, multiple sclerosis
IMID, immune-mediated inflammatory disease

Supplementary Table 2 Demographics according to IBD

Parameter	Ulcerative colitis (n=58)	Crohn's disease (n=96)	P-value
Presence of covariates (n, %)			
Corticoids at baseline	41 (71)	41 (43)	<0.001
Allergy	13 (22.4)	28 (29.2)	0.358
Associated IMIDs	9 (16.7)	21 (22.3)	0.409
Blood eosinophilia (n, %)			0.2
No	42 (72.4)	78 (81.3)	
Yes	16 (27.6)	18 (18.8)	
Persistent BE (n, %)			0.187
No	50 (86.2)	89 (92.7)	
Yes	8 (13.8)	7 (7.3)	
Tissue eosinophilia (n, %)			0.183
No	33 (60)	52 (71.2)	
Yes	22 (40)	21 (28.8)	

Supplementary Table 3 Eosinophilia pattern

Parameter	Biologic responders (n=92)	Biologic failure (n=62)
Single time eosinophilia	9 (9.8)	10 (16.1)
Persistent BE-2 times	4 (4.3)	3 (4.8)
Persistent BE -3 times	0 (0)	6 (9.7)
Persistent BE - 4 times	2 (2.2)	0 (0)

BE, blood eosinophilia

Supplementary Table 4 Association between corticoids and outcome during time

Parameter	Biologic responders (n=92)	Biologic failure (n=62)	P-value
Corticoids at baseline	47 (51.1)	35(56.5)	0.513
Corticoids at 8-14	14 (15.9)	22 (35.5)	0.006
Corticoids at 16-32	8 (10 .3)	12 (23.1)	0.047
Corticoids at 48-52	4 (5)	3 (8.3)	/

Supplementary Table 5 Logistic regression model for hospitalization and surgery

Hospitalization table

Variable	OR	95%CI	P-value
BE (yes/no)	1.91	0.75-4.66	0.17
Persistent BE (yes/no)	2.52	0.73-7.83	0.14
Tissue eosinophilia (yes/no)	0.84	0.30-2.16	0.72

Surgery table

Variable	OR	95%CI	P-value
BE (yes/no)	2.13	0.61-6.66	0.22
Persistent BE (yes/no)	2.91	0.60-11.0	0.17
Tissue eosinophilia (yes/no)	1.35	0.33-5.01	0.66

OR, odds ratio; CI, confidence interval; BE, blood eosinophilia

Supplementary Table 6 Logistic regression model according to biologics

VDZ table

Variable	OR	95%CI	P-value
BE (yes/no)	2.81	1.01, 8.10	0.047
Persistent BE (yes/no)	2.93	0.66, 15.3	0.16
Tissue eosinophilia (yes/no)	2.28	0.83, 6.44	0.11

IFX table

Variable	OR	95%CI	P-value
BE (yes/no)	1.82	0.54, 6.26	0.33
Persistent BE (yes/no)	2.00	0.41, 10.8	0.38
Tissue eosinophilia (yes/no)	1.57	0.52, 4.77	0.42

OR, odds ratio; CI, confidence interval; BE, blood eosinophilia

Supplementary Table 7 Logistic regression model for subtype of inflammatory bowel disease

CD patients

Variable	OR	95%CI	P-value
BE (yes/no)	2.97	1.05, 8.91	0.040
Persistent BE (yes/no)	2.16	0.45, 11.5	0.33
TE (yes/no)	2.13	0.77, 6.12	0.15

UC patients

Variable	OR	95%CI	P-value
BE (yes/no)	1.63	0.50, 5.28	0.41
Persistent BE (yes/no	2.72	0.60, 14.5	0.19
TE (yes/no)	1.75	0.59, 5.33	0.32

OR, odds ratio; CI, confidence interval; BE, blood eosinophilia; TE, tissue eosinophilia