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Blood eosinophilia as a marker of early and late treatment failure in severe acute exacerbations of COPD

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ABSTRACT

Background: Blood eosinophilia is frequently encountered in patients with AECOPD. However the impact of blood eosinophilia at admission in patients with AECOPD on outcome on the short and long term has not been extensively studied which was the objective of the present study.
Methods: We used data of 207 exacerbations from a randomized clinical trial on antibiotic prescription based upon CRP-levels *versus* GOLD guided strategy and analyzed the impact of blood eosinophils (≥2% of total white cell count and eosinophil count ≥300 cell/microliter) on clinical outcome.
Results: 207 patients were included of whom 39 (18·8%) had eosinophilia ≥2%, 23 patients (11.1%) had blood eosinophil ≥300 cell/microliter. Eosinophilia was associated with shorter median length of stay in the eosinophilic groups(≥2% and ≥300 cell/microliter) compared to the non-eosinophilic groups. Early treatment failure was reduced in the both the eosinophilic groups (≥2% and ≥300 cell/microliter). Late treatment failure (day 11–30) did not differ between the groups. Relapse, was more frequent the eosinophilic groups (≥2% and ≥300 cell/microliter), however in the latter group this did not reach statistical significance. Eosinophilia ≥2% was a risk factor for having relapse (eosinophilia ≥2%: HR = 2·351; 95%CI 1·335–4·139), whereas eosinophilia <2% was associated with a lower risk factor for having early treatment failure (HR = 0·339 95%CI 0·122–0·943).
Conclusion: We showed that blood eosinophilia at admission in patients with an AECOPD is associated with higher short-term treatment success rate. However, blood eosinophilia ≥2% predicts a less favorable outcome due to an increased risk of relapse.
Clinical Trial registration: NCT01232140.

1. Introduction

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) are associated with significant morbidity and mortality [1]. Current guidelines advocate the use of systemic corticosteroids in all exacerbations of COPD to shorten recovery time, improve arterial hypoxemia, improve lung function, decrease length of stay and reduce treatment failure [1–4]. Yet, these benefits are limited and systemic steroids have no effect on mortality, while they are associated with significant side effects [4]. Exacerbations are heterogeneous with respect to etiology and so is airway inflammation, which accompanies exacerbations [5]. Most exacerbations are associated with neutrophilic airway inflammation, but a significant proportion of exacerbations shows eosinophilic airway inflammation [5]. It has been demonstrated that patients with stable COPD and eosinophilic airway inflammation respond well to systemic glucocorticoid therapy [6]. A recent trial showed that peripheral blood eosinophil count exceeding ≥2% of total white blood cell

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List of abbreviations

AECOPD	acute exacerbation of COPD
WBC	total white blood cell count
OCS	oral corticosteroids
CRP	C-Reactive Protein
GOLD	Global Initiative for Chronic Obstructive Lung Disease
ICS	inhaled corticosteroids
GM-CSF	granulocyte-macrophage colony-stimulating factor

count (WBC) can be used to direct systemic corticosteroid treatment during an AECOPD [7]. In a subgroup analysis of another study it was also shown that patients with blood eosinophilia benefit most from treatment with corticosteroids compared to non-eosinophilic patients [8]. As blood eosinophil count seems a valid biomarker of eosinophilic airway inflammation, this raises the question whether blood eosinophilia can also be used to predict outcome in patients who are hospitalized with severe AECOPD [5]. We hypothesized that blood eosinophilia ≥2% of WBC as well as ≥300 eosinophils cell/microliter is associated with an improved response to systemic corticosteroids in patients with severe AECOPD resulting in a shortened length of stay (LOS), compared to otherwise well-matched patients with AECOPD without blood eosinophilia. In addition, we investigated whether blood eosinophilia is related to the occurrence of early and late treatment failure as well as relapse after 30 days. Some of the results of these studies have been previously reported in the form of an abstract [9].

2. Methods

Two hundred and nine participants were enrolled, 183 at the Northwest Clinics in Alkmaar, and 26 in the Medisch Spectrum Twente, Enschede, the Netherlands between July 2011 and September 2014, as part of the CRP-guided Antibiotic Treatment for acute exacerbations of COPD admitted to Hospital (CATCH) study. The methods and design of this trial have been described in detail and can be found at clinicaltrials.gov (NCT01232140). The local ethics boards approved the study protocol, and all patients provided written informed consent. Patients in this study were randomized to receive antibiotics or not, based on either C-Reactive Protein (CRP) levels or on GOLD criteria [1]. In the CRP group a cut-off level of ≥50 mg/L was used. In the GOLD group, patients with increased sputum purulence were prescribed antibiotics [1]. The main outcome in this study was the reduction of antibiotic consumption. Apart from antibiotics patients with an AECOPD were treated with oral corticosteroids (OCS) for 10 days (first 3 days 60 mg and last 7 days 30 mg of prednisolone). The study population consisted of patients diagnosed with COPD stages I–IV as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD), with an acute exacerbation as defined by GOLD [1]. Inclusion criteria were: age above 40 years; AECOPD requiring hospital admission according to GOLD guidelines, and former or current smokers with a minimum smoking history of 10 pack years [1]. Exclusion criteria were: pre-treatment with oral corticosteroids exceeding a total dose of 210 mg prednisolone during the last 14 days preceding the presentation with AECOPD for hospitalization, this was done to exclude patients with a chronic exacerbation of COPD. Other exclusion criteria consisted of pneumonia visualized on a chest X-ray, Immunocompromised patients, patients with active lung cancer and patients with pulmonary embolism were excluded.

3. Blood eosinophilia

Blood was collected at admittance, in K2EDTA tubes (Vacutainer, Becton Dickinson, Plymouth, UK). Peripheral blood smear were measured using a Sysmex XE-2100 Hematology Analyzer (Sysmex Corporation, Kobe, Japan) for cell differentiation.

Patients were grouped according to blood eosinophil count: ≥2% or <2%. For the purpose of a subgroup analysis a new group was created within the group of patients with blood eosinophilia ≥2% consisting of patients with eosinophil count ≥4%. Based upon earlier studies we also performed an analysis of absolute eosinophil count ≥300 cell/microliter [10–12].

4. Definition of clinical outcome

Treatment failure was defined as absence of resolution of symptoms and signs, worsening of symptoms and signs, occurrence of new symptoms and signs associated with the primary or a new infection, or death after randomization in the study [13]. Early treatment failure was defined as treatment failure within 10 days, late treatment failure was defined as treatment failure between day 11 and 30. Relapse was defined as a new exacerbation requiring antibiotics or systemic corticosteroids between day 31 and day 180.

5. Statistical analysis

SPSS, version 22.0 for Windows (IBM Corporation, Armonk NY) was used for data management and statistical analysis. Data are presented as median ± IQR unless stated otherwise. Differences between continuous variables were tested with students T-test or Mann-Whitney *U* test when appropriate; categorical variables were tested with the Pearson χ^2 test. Cox proportional hazard models were used to assess the association between eosinophil count group and treatment failure rates. Kaplan Meyer curves were used to display the association between eosinophilia and treatment failure. All tests were 2-sided with a p-value for significance of <0.05.

6. Results

6.1. Patients characteristics

We included 209 patients in the study (Fig. 1).

All patients were hospitalized with an AECOPD. The mean follow-up was 174 days (SD 30 days). Two of these patients were excluded because no blood was tested for eosinophils at admittance. Fourteen (6·7%) patients died during follow-up of 180 days. Thirty-nine (18·8%) patients had peripheral blood eosinophil counts ≥ 2%. Of this group 16 patients(7.7%) had a peripheral blood eosinophil counts ≥ 2% of WBC but without an absolute eosinophilic blood count ≥300 eosinophils/microliter. Twenty-three patients (11.1%) had a peripheral blood eosinophil counts ≥ 2% as well as an absolute eosinophilic blood count ≥300 eosinophils/microliter.

In the eosinophilic group>2%, the median eosinophil count was 3·1% (IQR 2·6–4·9%), whereas in the non-eosinophilic group (<2% eosinophils) this was 0·1% (IQR 0·0-0·5%). Absolute median eosinophil count in the eosinophilic group was $0{\cdot}37 \times 10^9$/L (IQR $0{\cdot}21–0{\cdot}53 \times 10^9$/L) and in the non-eosinophilic group $0{\cdot}01 \times 10^9$/L (IQR $0{\cdot}00\text{-}0{\cdot}05 \times 10^9$/L) [$p < 0{\cdot}001$]. Baseline characteristics are outlined in Table 1.

Absolute number of eosinophils as well as percentage eosinophils of WBC did not differ between patients with and without

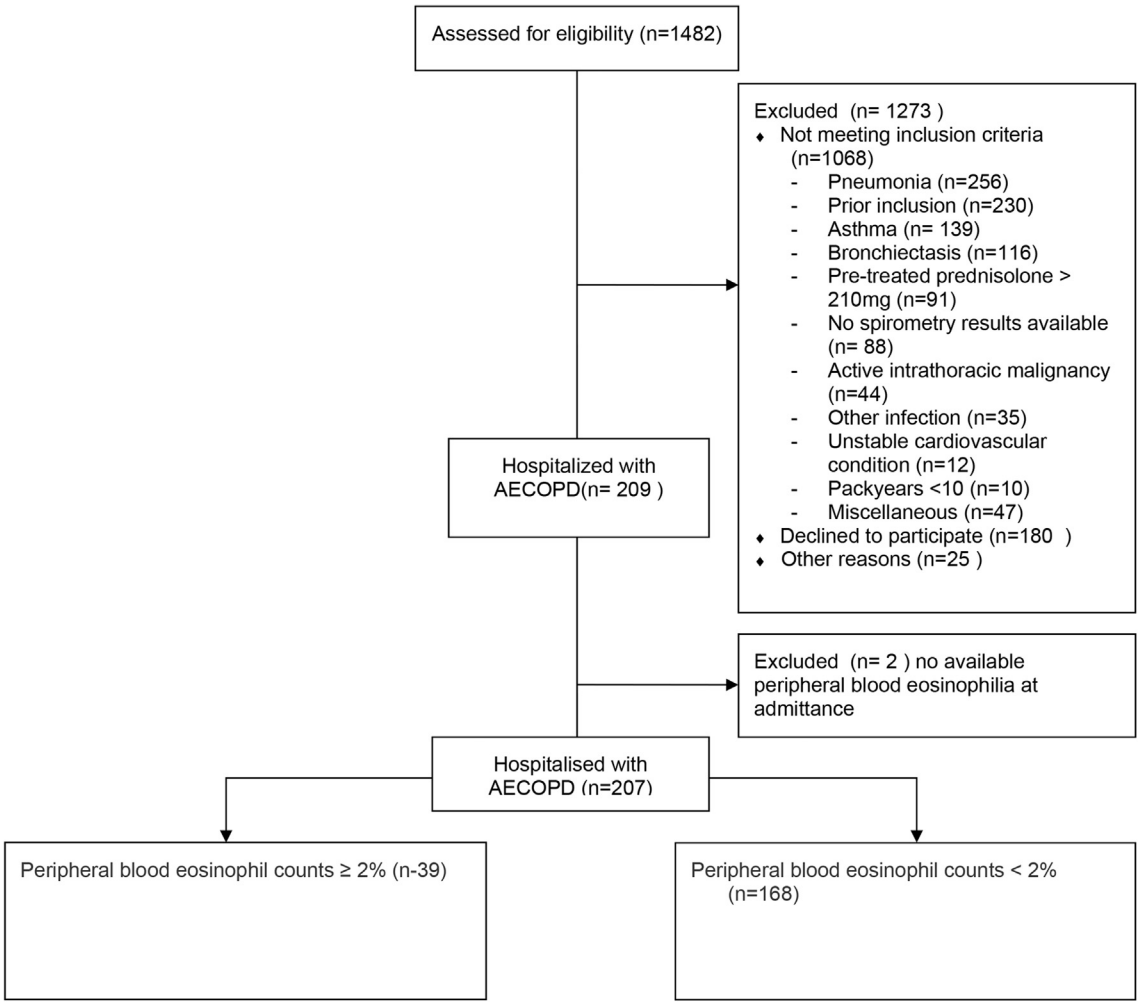


Fig. 1. Trial profile.

Table 1
Baseline characteristics.

	Blood eosinophils		
	≥2% (n = 39)	<2% (n = 168)	p-value
Age, years (mean, sd)	70.4 (8.7)	69.7 (11.5)	0.721
Gender, % male	59.0	46.4	0.158
Absolute eosinophil count (x10^9/L, IQR)	0.37(0.21–0.53)	0.01(0.00–0.05)	0.000
Peripheral blood Eosinophilia (%, IQR)	3.1% (2.6–4.9)	0.1(0.0–0.5)	0.000
BMI[a], kg/m^2 (mean, SD)	25,3 (5.0)	24,9 (5.3)	0.693
Pack years, (median, IQR)	40 (29–60)	40 (25–50)	0.255
Current smoker, n (%)	9 (23.1)	60 (35.9)	0.126
Number of exacerbations in the past two years, n (median, IQR)	3 (1–6)	3 (1–4)	0.502
Pretreatment oral corticosteroids, n (%)	16 (41.0)	87 (51.8)	0.226
Cumulative oral corticosteroid dose last 14 days, mg (median, IQR)	105(70–165)	90(60–180)	0.966
Inhaled corticosteroids, n (%)	28 (71.8)	144 (85.7)	0.037
Cumulative inhaled corticosteroid dose ug (median, IQR)	500(400–1000)	675(400–1000)	0.520
Antibiotics at admission, n (%)	11 (28.2)	65 (38.7)	0.140
FEV1[b], liters (mean, SD)	1.31 (0.48)	1.15 (0.50)	0.069
FEV1% pred, (mean, SD)	50.6 (16.0)	44.6 (16.6)	0.064
FVC[c], liters (mean, SD)	3.0 (1.0)	2.7 (1.0)	0.143
FVC % pred, (mean, SD)	89.0 (23.9)	83.4 (21.0)	0.152
FEV1/FVC %, (mean, SD)	42.5 (13.6)	39.9 (12.4)	0.248

[a] BMI: body mass index (kg/m^2).
[b] FEV1: forced expiratory volume 1 s.
[c] FVC: Forced Vital Capacity, SD: standard deviation, IQR: inter quartile range.

pretreatment with systemic corticosteroids: in the pretreated group the median absolute eosinophil count was 0·01 × 10^9/L (IQR 0·00-0·15 × 10^9/L) and in the non-pretreated group median 0·04 × 10^9/L (IQR 0·00-0·16 × 10^9/L; p = 0·157). Similarly, the percentages eosinophils were 0·1% (IQR 0·0–1·4%) and 0·04% (IQR 0·0–1·7%; p = 0·09), respectively. Baseline characteristics did not differ in the absolute eosinophil count ≥300 cell/microliter group compared to <300 cell/microliter group. (data not shown).

6.2. Length of stay and mortality

The median length of stay was 5 (IQR 4–6) days in the eosinophilic group as compared to 7 (IQR 5–10) days (p = 0.001) in the non-eosinophilic group. In-hospital mortality was numerically higher in the non-eosinophilic group, 5 patients (3%) died as compared to the eosinophilic group none died (0%) (p = 0.275). During the follow-up of 180 days mortality rate was similar in both groups: in the non-eosinophilic group 12 (7.1%) patients died, in the eosinophilic group 2 (5.1%, p = 0.652). Results regarding the patients with an eosinophilic blood count ≥300 and <300 eosinophils/microliter can be found in Table 2.

6.3. Treatment failure

Treatment failure rates for eosinophilia ≥2% and <2% as well as total blood eosinophilia ≥300 and <300/microliter are depicted in Fig. 2 and were markedly different over time.

Early treatment failure rates were higher in the non-eosinophilic group 46 (27·4%) compared to 4 (10·3%) patients in the eosinophilic group (p = 0·024) (supplemental data figure E1). Late treatment failure rates were equal: 10 (28·6%) patients had treatment failure in the eosinophilic group and 32 (26·2%) patients in the non-eosinophilic group (p = 0·783) (supplemental data figure E2). Relapse rates were higher in the eosinophilic group with 18 (72·0%) patients compared to 38 (42·2%) patients in the non-eosinophilic group (p = 0·008) (supplemental data figure E3). The median total number of treatment failure events measured after 180 days post-inclusion was also higher in the eosinophilic group with 2 (IQR 1–2) events compared to 1 (IQR 0–2) event in the non-eosinophilic group (p = 0·042). Results regarding treatment failure and relapse in the patients with an eosinophilic blood count ≥300 and <300 eosinophils/microliter can be found in Table 2.

Cox proportional hazard analysis revealed that eosinophilia (≥2%) at admittance was associated with a lower risk factor for having treatment failure in the first 10 days (hazard ratio HR = 0·339 95%CI 0·122–0·943). Eosinophilia at admittance was not a risk factor for developing late treatment failure (hazard ratio for eosinophilia ≥2% = 1·094 95%CI 0·538–2.225; p = 0·804). Blood eosinophils ≥2% at admittance was a risk factor for relapse (hazard ratio for eosinophilia ≥2% = 2·351; 95%CI 1·335–4·139).

6.4. Increased eosinophilia

In the group of patients with eosinophilia ≥2%, 26 (66·7%) patients had eosinophil percentages between 2 and 4% and 13 (33·3%) patients had ≥4%. Early treatment failure rate was not different between ≥4% eosinophil group (1 patient 7·7%) compared to the eosinophilia 2–4% group (3 patients 11·5%) (p = 0·709). However, late treatment failure was higher in the ≥4% eosinophil group, which was observed in 6 patients (50%) as compared to 4 patients (17·4%), p = 0·043) in the 2–4% eosinophil group. Relapse rates were lower in the ≥4% group compared to the 2–4% group, respectively 2 (33·3%) patients and 16 (84·2%) patients (p = 0·016). Overall treatment failure was not different in patients with ≥4% eosinophils, 9 (69·2%) patients compared to patients with an eosinophilia 2–4%, 23 (88·5%) patients (p = 0·140).

7. Discussion

This study demonstrates two important new findings related to blood eosinophilia, which was present in 19% of patients with an AECOPD at presentation to the hospital regardless whether they were pre-treated with systemic corticosteroids or antibiotics: better short-term treatment response, but more exacerbations in the 31–180 days thereafter although the latter was not observed in the eosinophilic group ≥300 eosinophils/microliter. Eosinophilia was also associated with a shorter length of hospital stay, as was also observed in another study [14].

The decrease in early treatment failure in the eosinophilic group might be explained by the observation that oral corticosteroids had a more prominent effect in patients with eosinophilic inflammation [7]. Similarly, discontinuation of oral corticosteroids may lead to a surge in circulating eosinophils and accumulation of eosinophils in the bronchial mucosa and underlies a new exacerbation and thus an increased relapse rate [15,16]. This is further supported by the finding that patients with a relatively high number of circulating eosinophils (≥4%) were more likely to experience late treatment failure. In another study no increased relapse rates were observed in eosinophilic patients, which may have been due to exclusion of patients with more than 4 hospitalizations for any reason [14]. This might have led to an under-representation of patients with high eosinophilia and frequent exacerbations. The increased number of relapse exacerbations in the eosinophilic group are in line with an earlier study and might partly be explained by the fact that in our study in the eosinophilic group less patients were treated with ICS [17]. An earlier study showed that ICS might lower the exacerbation frequency in patients with eosinophilia [18]. The observation that an increase in relapse was not seen in the absolute eosinophil count ≥300 cell/microliter group might be explained by the small sample size.

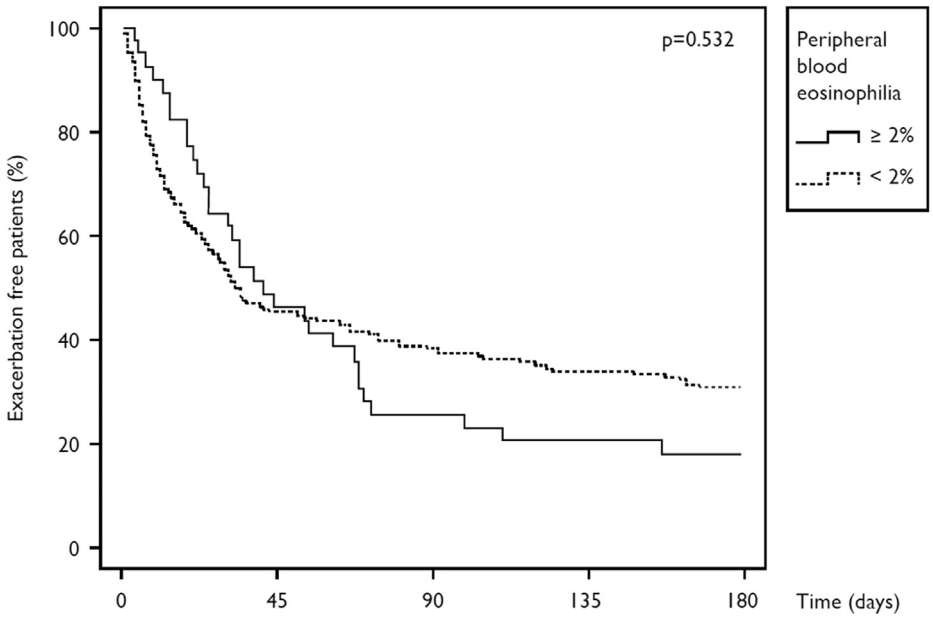
Nineteen percent of our patients had blood eosinophilia at baseline despite the use of systemic steroids in the last two weeks in 41%. This signifies that systemic steroids do not fully abrogate

Table 2
Results absolute eosinophil count.

	Eosinophils ≥300/microliter (n = 23)	Eosinophils <300/microliter (n = 184)	p value
Length of stay	7(5–10)	4(4–6)	**0.012**
Early treatment failure n,(%)	1(4.3)	49(26.6)	**0.019**
Late treatment failure n,(%)	7(31.8)	35(25.9)	0.563
Relapse n,(%)	10(66.7)	46(46)	0.135
Number of exacerbations	1(0–2)	0(0–1)	0.174
Mortality n,(%)	1(4.3)	13(7.1)	0.652
In hospital mortality n,(%)	0(0)	5(2.7)	0.424

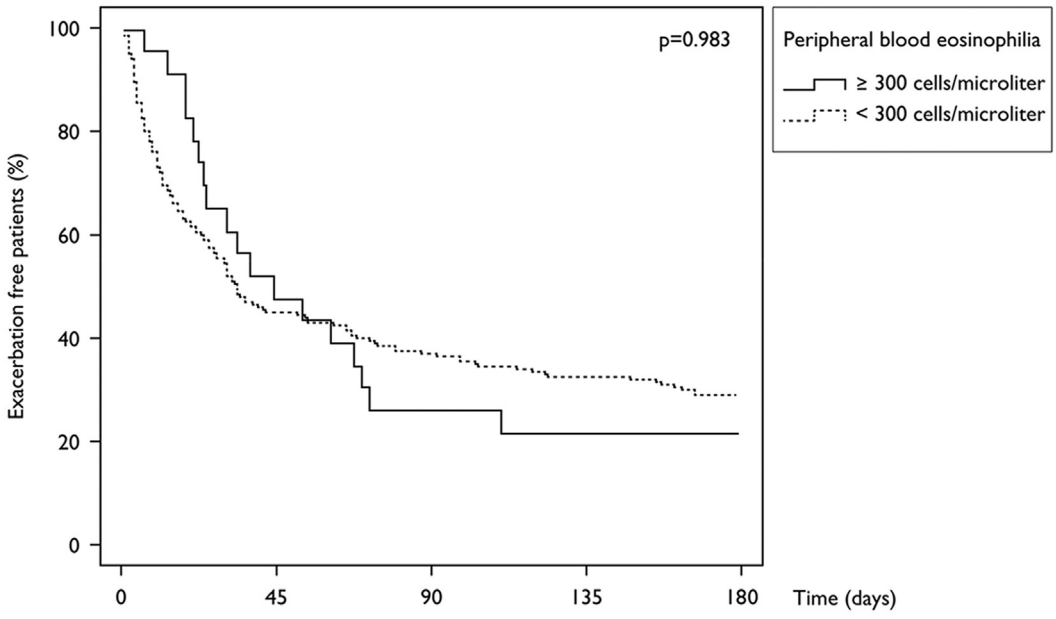
All data are represented as median (IQR) unless specified otherwise.

a



No. at risk					
Blood eosinophils ≥ 2%	39	18	10	8	7
Blood eosinophils < 2%	168	76	64	57	52
No of exacerbations					
Blood eosinophils ≥ 2%	0	21	29	31	32
Blood eosinophils < 2%	0	92	104	111	116

b



No. at risk					
Blood eosinophils ≥ 300 cells/microliter	23	11	6	5	5
Blood eosinophils < 300 cells/microliter	184	83	68	60	54
No of exacerbations					
Blood eosinophils ≥ 300 cells/microliter	0	12	17	18	18
Blood eosinophils < 300 cells/microliter	0	101	116	124	130

Fig. 2. a)Kaplan Meyer Curve day 0–180 eosinophilia≥ 2% and <2%. b)Kaplan Meyer Curve day 0–180 eosinophilia≥ 300 and <300 eosinophils/microliter.

blood eosinophilia.

It is still unclear how eosinophils contribute to the pathogenesis of AECOPD. Eosinophils can release granular contents that contain cytotoxic and inflammatory mediators. Activated eosinophils are also an important source of reactive oxygen species, which together with the granular contents induce local tissue damage and direct immune response [19]. It is currently unknown what causes the recruitment and possibly activation of eosinophils during AECOPD, but there are several possible candidate mediators that are associated with exacerbations. IL-33 is an alarmin, which is released during virus-induced exacerbations, and has been shown to recruit and activate eosinophils [20]. Likely, IgA directed against microorganisms will increase and may lead to enhanced secretory IgA and secretory component. Both IgA and secretory component are potent activators of eosinophils [21–23]. Eosinophils might also contribute to the pathogenesis of COPD by a defective efferocytosis of apoptotic eosinophils, leading to an increased number of sputum eosinophils. Subsequently, with failure of the apoptotic pathway, these eosinophils become necrotic and release toxic intracellular pro-inflammatory mediators leading to more influx of eosinophils. An increase of defective efferocytosis has been related to severity and frequency of COPD exacerbations [24]. Which of these processes or whether other mechanisms are involved awaits further studies.

Eosinophils are derived from the bone marrow under the influence of granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-3 and IL-5, with IL-5 as most specific to the eosinophil lineage [25,26]. IL-5 is also known for its pivotal role in homing, activation and prevention of apoptosis of eosinophils [26–28]. Therefore, IL-5 cytokine and IL-5-receptor blocking agents are of interest to reduce eosinophilic inflammation. Recently, benralizumab, an anti-interleukin-5 receptor monoclonal antibody has been investigated in patients with stable COPD and sputum eosinophilia [10]. Benralizumab was able to reduce the number of eosinophils in blood and sputum effectively, but failed to reduce the exacerbation rate. In a post-hoc subgroup analysis, patients with peripheral blood eosinophil count exceeding 200 cells per μL had fewer exacerbations, improved health status, symptoms and lung function [10]. This, however, does not exclude a potential role for these biologics after treatment for an exacerbation, preventing relapses upon withholding oral corticosteroids.

The strength of the present study is that this is the first study in which all the patients received a standardized corticosteroid treatment, which provides a unique insight into the role of eosinophils in AECOPD. Moreover, the fact that only 2 patients were excluded from the present study due to missing data, makes the risk of a selection bias small. Another strong point of this study is the fact that all patients had a known history of COPD confirmed by spirometry and a smoking history of at least 10 pack-years. Patients with a prior history of asthma or other respiratory disease were excluded leaving a homogeneous population of patients with COPD. Yet, we cannot entirely rule out the possibility that some patients who were included in this study did have a form of atopy or asthma in their childhood.

The present study also has several limitations. First, the study was not primarily designed to investigate the effect of peripheral blood eosinophilia as a biomarker for outcome of AECOPD. The results should therefore be interpreted with caution and this study should be regarded as exploratory. Secondly, the percentage of patients treated with inhaled corticosteroids before admittance in the non-eosinophilic group was slightly but significantly higher, which may have influenced the number of blood eosinophils at baseline in the non-eosinophilic group [29]. Another potential pitfall is the high number of patients pretreated with systemic corticosteroids. Systemic corticosteroids can lower the number of circulating eosinophils leading to a lower percentage of eosinophils and can increase the number of circulating neutrophils [7,30]. Therefore, due to the pretreatment with corticosteroids a shift of patients from the eosinophilic group into the non-eosinophilic group might have occurred leading to an underestimation of the observed effects. This is further emphasized by the fact that on day 30 there was a significant increase in the absolute numbers of eosinophils as well as an increase of the percentage eosinophils of WBC compared to day 0 in non-eosinophilic patients (data not shown).

8. Conclusions

In this study we have observed that blood eosinophilia at admittance is associated with a shorter length of stay and lower 10-days failure rate. However, compared to the group with eosinophils <2%, the group with eosinophilia had higher long-term relapse rates after stopping systemic corticosteroids although this did not reach significance in the >300 eosinophils/microliter. We suggest that peripheral blood eosinophilia indicates a distinct phenotype in COPD and it would be of interest to investigate in a randomized study whether initiation and continuation of corticosteroid therapy in patients hospitalized with AECOPD can based upon peripheral blood eosinophilia.

Competing interests

HJP, RD, MGG, PVV, JMD, TSW and WGB have no conflict of interest. RL has received funding from the Lung Foundation (3.2.10.69) (the Netherlands) and GSK (CTR 114696) to study anti-IL-5 treatment in relation to RV16-induced exacerbations of asthma, all not related to this submitted work. HAK's institution has received grants and fees for consultancies from Novartis, GlaxoSmithKline, Fluidda, AstraZeneca, and Boehringer Ingelheim outside the submitted work.

Author's contributions

HJP contributed to the conception and design of the study, data collection, interpretation, data analysis and manuscript writing.

RD contributed to data collection and manuscript writing.

WGB contributed to conception and design of the study, data analysis and manuscript writing.

JMD contributed to conception and design of the study and manuscript writing.

PVV and MGG contributed to data collection and manuscript writing.

RL, HAK and TSW contributed data analysis and manuscript writing.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.rmed.2017.07.064.

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