Blood Eosinophil Count Stability in COPD and the Eosinophilic Exacerbator Phenotype

Federico Baraldi[1,2], Samuel Bartlett-Pestell[1], James P Allinson[1], Mairi Macleod[1], Jordina Mah[1], Chloe Bloom[1], Aaron Brady-Green[1], Apolline Marion[1], Alberto Papi[2], Jadwiga A Wedzicha[1], Lydia J Finney[1]

[1]National Heart and Lung Institute, Imperial College London, London, United Kingdom

[2]Department of Respiratory Medicine, University of Ferrara, Ferrara, Italy

Corresponding author: Dr Lydia Finney, National Heart and Lung Institute, Imperial College London, London, United Kingdom

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Email: l.finney@imperial.ac.uk

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To the Editor:

Chronic obstructive pulmonary disease (COPD) is a complex and heterogeneous condition. Blood eosinophil count (BEC) has been established as a biomarker which can predict response to inhaled corticosteroids (ICS)(1) with 300 cells/µL or 100 cells/µL being adopted by international guidelines(2). Eosinophilic COPD is increasingly recognised as a distinct phenotype(3). However, questions remain regarding whether this phenotype carries an increased risk of exacerbations, and which targeted Th2 biologic treatments may be most effective(4). A potential challenge when linking BEC to clinical outcomes is the degree to which BEC varies across months, seasons and even throughout the day(5–7).

The aims of this study were to evaluate stability of the eosinophilic phenotype over time and to investigate the relationship between BEC and exacerbations**.** Some of the results of this study have been previously reported in the form of an abstract(8).

Methods

Objectives and Study Population: To evaluate the stability of the eosinophilic phenotype in COPD, we conducted a longitudinal analysis from the London COPD Exacerbation Cohort (EXCEL Cohort). All participants gave written informed consent, and the protocol was approved by Hampstead Ethics Committee (Ref 09/H0720/8)(9). At recruitment participants had non-reversible airflow obstruction (FEV1/FVC < 0.7), a smoking history of at least 10 pack years and no other concomitant lung diseases. Participants were excluded if they had a clinician diagnosis of asthma or reversible airflow obstruction defined as ≥ 200 ml or ≥12% increase in FEV1 following 400 µg Salbutamol(10). COPD patients were reviewed every three to six months at their clinical baseline (including clinical assessment, spirometry measurement, collection of quality-of-life questionnaires, blood, and sputum). Participants were instructed to contact the study team within 48 hours of exacerbation onset for clinical assessment before starting exacerbation treatment. A blood test for full blood count was taken before treatment with oral corticosteroids or antibiotics for all exacerbations reported to the study team.

For each participant, data was collected from 4 annual visits during stable state (V1-V4). Participants were included if they had an annual review visit in 2022. Baseline demographic data was collected at each stable visit. Data was also collected from exacerbation visits, according to previously published criteria(10), before the initiation of any corticosteroid treatment.

Eosinophilic Subgroups: A BEC cut-off of 300 cells/µL was used to classify "BEC Low" or "BEC High" conditions at all stable visits. Based on stable BEC values, we defined three subgroups: the "Persistent group", characterized by at least 3 annual stable visits (out of 4) with BEC ≥ 300 cells/µL; the "Intermittent group", with 1 to 2 annual stable visits with BEC ≥ 300 cells/µL; and the "Never group", with no eosinophilic annual stable visits. Additionally, within each group, we identified a subgroup of "Eosinophilic Exacerbators," characterized by at least one exacerbation visit with BEC ≥ 300 cells/µL. Participants were defined as "Non-Eosinophilic Exacerbators" if they had no exacerbation visits with a BEC ≥ 300 cells/µL during the study period.

Statistical Analysis: For comparing data which were not normally distributed between two groups, the Mann-Whitney test was employed. For the comparison of categorical data between more than two groups, a Chi-squared test was applied. To investigate whether Eosinophilic Exacerbators had more frequent exacerbations compared to Non-eosinophilic Exacerbators during the study a mixed-effects Poisson model was applied, with random effects accounting for repeat exacerbations in the same patient. To evaluate whether Eosinophilic Exacerbators had a higher mean baseline CAT score compared to Non-Eosinophilic Exacerbators, a mixed-effects linear model with a compound symmetry covariance structure was used to account for repeated CAT score measures with whilst also accounting for exacerbation frequency within the model. All statistical analyses were performed using STATA BE/18.0.

Results:

Patient Characteristics: There were 100 patients included in the study (42% female). Median age was 71.4 ± 7.1 years, mean pack/year history was 48.4 ± 27.4 and 78% were ex-smokers. The mean

total number of annual exacerbations was 1.37 ±1.30 per year. Demographics are shown in Table 1.

BEC variations during the annual baseline visits are represented in Figure 1 by a Sankey diagram showing the fluctuation of the eosinophilic status over time. At V1, 35% of patients were classified as “High BEC” and 65% as “Low BEC.” Across each respective annual baseline visits, the number of patients with “High BEC” progressively decreased by 50%, 40%, and 35%. At the end of the analysis, 18% were defined as “Persistent Eosinophilic,” 29% as “Intermittent Eosinophilic,” and 53% as “Never Eosinophilic.” Within these groups respectively we identified 89%, 51%, and 26% of subjects experiencing at least one eosinophilic exacerbation (Figure 1).

Exploring the potential for missing a high baseline eosinophil phenotype if classification were based upon one visit rather than all four visits during our follow-up, we found that 21.4%, 7.1%, 28.5%, and 21.4% of the “Persistent High” group members would be classified as having Low BEC at V1, V2, V3, and V4 respectively.

Associations of Stable Eosinophilic Groups with Clinical Outcomes: To evaluate the effect of ICS on eosinophilic status, we assessed inhaled corticosteroid use either in association with LABA or with LABA plus LAMA in each group. At V1, 61% of the Persistent, 41% of the Intermittent, and 56% of the Never group were treated with an ICS (p=0.32). There were 7 patients “High BEC” at V1 not receiving an ICS. In this group, we analysed changes in BEC values and number of exacerbations after the initiation of ICS. At the consecutive visit (V2) there was a median decrease in BEC of 197 cells//µL with initiation of ICS (95% CI -310.7 to –83.62.30; p<0.01). Exacerbations decreased by 1.71 exacerbations per year following the initiation of ICS treatment p<0.01.

There was no significant association between eosinophilic status and degree of airflow obstruction. Similarly, there was no relationship between the eosinophilic status and quality of life (CAT score) at stable condition when 1137 CAT scores were considered (95% CI -5.48 to 2.08 p=0.38).

The Eosinophilic Exacerbator Phenotype: Further evaluation of the clinical impact of the Eosinophilic Exacerbator phenotype over the course of the study was conducted using a mixed-effects model. The analysis revealed that the Eosinophilic Exacerbators group had a significantly higher mean CAT score in stable disease, with an increase of 2.82 points compared to the Non-Eosinophilic Exacerbators subgroup over the study (95% CI: 0.07-5.57, p = 0.04). Additionally, within the Eosinophilic Exacerbators group, there was a 60% (95% CI 10.04%-132.85%, p = 0.01) increased risk of annual exacerbations compared to the Non-Eosinophilic Exacerbation subgroup. Patients with a BEC>300 cells/µL at their first exacerbation also had a significantly higher exacerbation rate over the study period compared to COPD patients where the BEC was <300 cells/µL at their first exacerbation (4.1+/-2.5 v 3.0 +/-2.6 p=0.03).

Discussion

A deeper understanding of the eosinophilic phenotype in COPD is crucial to targeting existing treatments and identifying patients who are likely to respond to new biologics. Our study shows that 18% of the COPD population was persistently eosinophilic over time, with 29% fluctuating between high and low blood eosinophil counts. Stability in BEC is not currently considered within the inclusion criteria of clinical trials targeting the “Eosinophilic COPD phenotype.” We showed that a one-off BEC measurement can miss up to 29% of patients who would otherwise be defined as eosinophilic.

We identified a subgroup of Eosinophilic Exacerbators, in all three groups, with a higher CAT score and an increased risk of exacerbations compared to the Non-Eosinophilic Exacerbators. This represents a new group who may potentially respond to Th2 targeted biologic treatment. Limitations of this study include the relatively small size of the cohort and the lack of fractional exhaled nitric oxide (FeNO) as an alternative marker of Th2 inflammation. In addition, this is an unadjusted analysis and therefore further work is needed to evaluate whether high blood eosinophil count is independent of other known risk factors for COPD exacerbations. Further studies are needed to elucidate pathways of eosinophilic inflammation in COPD in the transition between stability and exacerbation to achieve a truly personalized treatment approach.

Table 1. Demographic details of COPD participants

Demographic	Persistent (n=18)	Intermittent (n=29)	Never (n=53)	Total (n=100)	*P* value
Age, mean (±SD)	73.3 (4.9)	71.5 (6.5)	70.6 (8.1)	71.4 (7.1)	0.65
Male sex, n (%)	13 (72.2)	19 (65.5)	26 (49.1)	58 (58)	0.14
Ex smokers, n (%)	12 (77.78)	23 (79.31)	41 (77.36)	78 (78)	0.97
Exacerbations, mean (±SD)	1.33 (0.9)	1.21 (1.0)	1.47 (1.7)	1.37 (1.3)	0.88
ICS treated, n (%)	11 (61.1)	12 (41.4)	30 (56.6)	53 (53)	0.32
Pack year, mean (±SD)	56.66 (32.8)	47.0 (31.2)	44.2 (22.4)	48.1 (27.4)	0.21
FEV1, % pp (±SD)	55.60 (14.3)	64.0 (23.9) (22.33)	63.8 (14.3)	63.1(20.1)	0.25

COPD participants were seen at 4 stable visits. Data presented are taken from visit 1 (V1). Data are presented as mean +/- standard deviation. Categorical variables unless otherwise stated. COPD participants were classified as “Persistent” if they had at least 3 annual visits (out of 4) with BEC ≥ 300 cells/μL; “Intermittent” with 1 to 2 annual visits with BEC ≥ 300 cells/μL; and “Never group”, if they had no stable visits with BEC ≥ 300 cells/μL. Numerical data with a normal distribution were analysed by ANOVA with a Tukey post-hoc correction. Data which were not normally distributed were analysed by Kruskal Wallis test with a Dunn’s post-hoc correction.

Figure 1

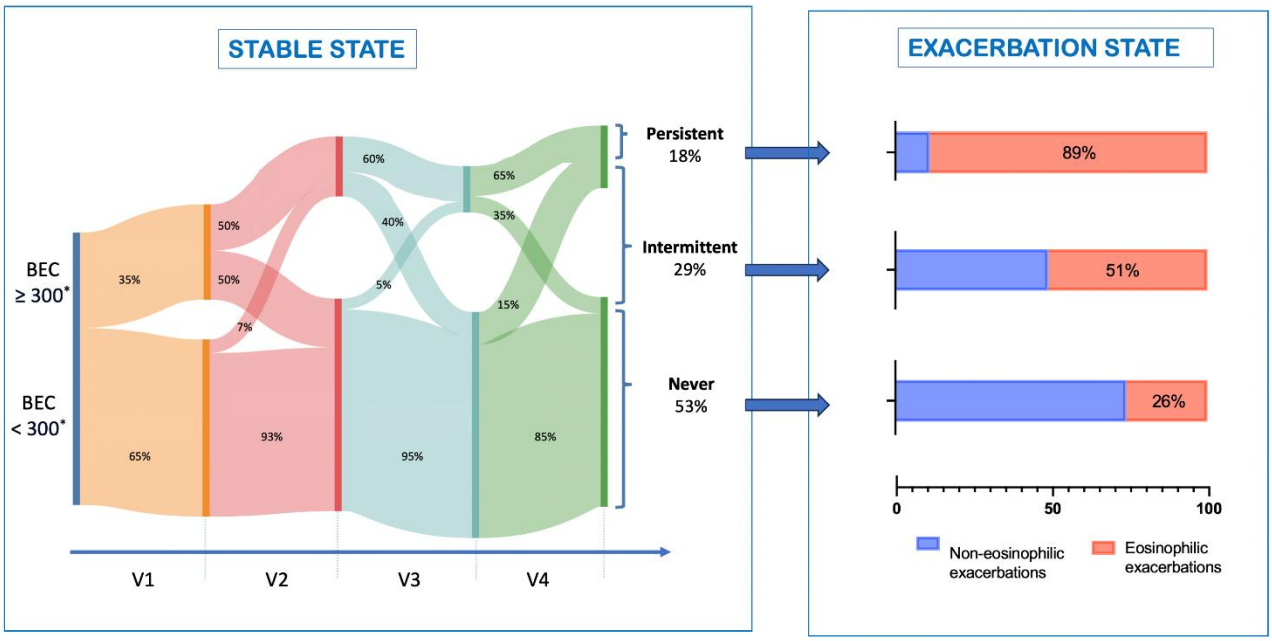
STABLE STATE
EXACERBATION STATE
BEC ≥ 300*
BEC < 300*
35%
65%
50%
50%
7%
93%
60%
40%
5%
95%
65%
35%
15%
85%
Persistent 18%
Intermittent 29%
Never 53%
89%
51%
26%
0
50
100
Non-eosinophilic exacerbations
Eosinophilic exacerbations
V1
V2
V3
V4

Figure 1 Legend

Stable State: The Sankey diagram shows the fluctuation of eosinophil levels over four annual baseline visits (V1 to V4). Each visit's time frame is represented by a different colour: V1 (orange), V2 (red), V3 (light blue), and V4 (green). V1 describes the first BEC collected, categorizing patients into two groups: High BEC (35%) and Low BEC (65%). At V2, 50% of patients initially classified as High BEC changed their status to Low BEC, while 7% of the Low BEC group transitioned to High BEC. At V3, 40% of the High BEC patients from V2 changed to Low BEC, and 5% of the Low BEC patients transitioned to High BEC. At V4, 35% of the High BEC patients from V3 switched to Low BEC, and 15% of the Low BEC patients transitioned to High BEC. The time frame for V1 is within 18 months before V2, while V2, V3, and V4 are each separated by 12 months. Three groups—Persistent (18%), Intermittent (29%), and Never (53%)—were defined based on the criteria detailed in the “Eosinophilic Subgroups” chapter.

Exacerbation State: The bar chart represents the eosinophilic and non-eosinophilic exacerbations observed during the exacerbation visits in each of the three groups defined as ‘High’, ‘Intermittent’ or ‘Low’ according to stable blood eosinophil levels throughout the study as described above.

* cells/µL

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192