Blood Eosinophil Count and Exacerbation Risk in Patients with COPD

Marjan Kerkhof[1], Dirkje S Postma[2], Guy Brusselle[3,4], Alvar Agusti[5], Antonio Anzueto[6], Rupert Jones[7], Alberto Papi[8], Ian D Pavord[9], Emilio Pizzichini[10], Todor Popov[11], Nicolas Roche[12], Dermot Ryan[13], Mike Thomas[14], Claus Vogelmeier[15], Alison Chisholm[16], Daryl Freeman[17], Mona Bafadhel[9], Elizabeth V Hillyer[1], David B Price[1,16,18] on behalf of the Respiratory Effectiveness Group

[1]Observational and Pragmatic Research Institute Pte Ltd, Singapore, SG;

[2]University of Groningen, University Medical Center Groningen, Department of Pulmonology, Groningen, the Netherlands;

[3] Department of Respiratory Medicine, Ghent University Hospital, Ghent, Belgium;

[4]Departments of Epidemiology and Respiratory Medicine, Erasmus Medical Center, Rotterdam, the Netherlands;

[5]Respiratory Institute, Hospital Clinic, IDIBAPS, Universitat de Barcelona, CIBERES, Spain;

[6]Department of Pulmonary/Critical Care, University of Texas Health Sciences Centre, and South Texas Veterans Healthcare System, San Antonio, USA;

[7]Plymouth University Peninsula Schools of Medicine and Dentistry, Plymouth, UK;

[8]Department of Medicine, University of Ferrara, Ferrara, Italy;

[9]Respiratory Medicine Unit, Nuffield Department of Medicine, University of Oxford, Oxford, UK;

[10]NUPAIVA (Asthma Research Centre), University Hospital, Federal University of Santa Catarina, Florianópolis, Santa Catarina, Brazil;

[11]Medical University Sofia, Sofia, Bulgaria;

[12]Cochin Hospital Group (AP-HP), University Paris Descartes (EA2511), Paris, France;

[13]Allergy and Respiratory Research Group, Usher Institute of Population Health Sciences and Informatics, University of Edinburgh, UK

[14]Primary Care and Population Sciences, University of Southampton, Aldermoor Health Centre, and NIHR Southampton Respiratory Biomedical Research Unit, Southampton, UK;

[15]Department of Medicine, Pulmonary and Critical Care Medicine, University Medical Center Giessen and Marburg, Philipps-University Marburg, Member of the German Center for Lung Research (DZL), Marburg, Germany;

[16]Respiratory Effectiveness Group, Cambridge, UK;

[17]Mundesley Medical Centre, Norfolk, UK;

[18]Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, UK.

Corresponding author: Prof David B Price, Academic Primary Care, Division of Applied Health Sciences, University of Aberdeen, Polwarth Building, Foresterhill, Aberdeen, UK AB25 2ZD; Tel +44 1224 554588; Fax +44 1224 550683; Email dprice@opri.sg

Source of support: Respiratory Effectiveness Group

Exacerbations in chronic obstructive pulmonary disease (COPD) are major contributors to worsening lung function, impaired quality of life, and emergency healthcare utilisation. COPD exacerbations are heterogeneous in terms of airway inflammation and aetiology and a recent study of 145 patients reported an eosinophilia predominant group constituting 28% of exacerbations [1]. About 60% of COPD patients have blood eosinophil counts of ≥2% and such counts appear associated with an increased risk of exacerbations [1-4]. However, the association between blood eosinophil counts measured at stable disease and COPD exacerbations in the subsequent year is not fully understood.

We performed a historical follow-up study using longitudinal medical record data to evaluate the potential of blood eosinophil counts as a biomarker of exacerbation risk by assessing the association between blood eosinophil levels measured when COPD was stable and the exacerbation rate in the subsequent year, in a broad COPD population. We also investigated whether the association significantly differed in specific patient subgroups defined by smoking status, gender, disease severity (GOLD groups A to D), or ICS treatment. Data was extracted from March 1994 to February 2014 from the United Kingdom (UK) Optimum Patient Care Research Database [5].

We evaluated patient characteristics during one baseline year before the index date, defined as the date of most recent eosinophil count at stable COPD with ≥1 follow-up year available. Comorbidities included as potential confounding factors were defined as those ever-recorded during the registration period and assessed at index date. Eligible patients were aged ≥40 years, had a recorded COPD diagnosis, no other chronic respiratory disease, including no asthma related Read code recorded ever, with at least one blood eosinophil count measured at stable disease (no COPD exacerbations 4 weeks before and after). Other eligibility criteria FEV_1/FVC <0.70 recorded within 5 years of index date, history of cigarette smoking (current and ex-smokers were included) and ≥1 year of data before and after index date. Eosinophil counts ranging from 0.05 to $<0.45x10^9/L$ were the reference category, low

counts were <0.05x10^9/L, and elevated counts ≥0.45x10^9/L, based on reference values (0.04–0.40 x10^9/L for adults) applied in UK laboratories [6]. Analyses were adjusted for the following potential confounders: gender, age, body mass index, smoking status, therapy and history of comorbidities associated with eosinophil counts. COPD exacerbations were defined as any of the following: unscheduled hospital admission or emergency department attendance, and/or an acute course of oral corticosteroids (OCS), and/or antibiotics prescribed at a lower respiratory consultation. The association of blood eosinophil counts with subsequent exacerbations rate was analyzed by estimating rate ratios (RRs) with 95% confidence intervals (CIs) using a quasi-Poisson regression model allowing for over-dispersion[7].

64,847 COPD patients were identified, of whom 8,318 were eligible. The mean (SD) age was 70 (10) years and 56% were men. Of these, 6,660 (80%) patients had mMRC scores available to determine GOLD groups A–D [8]. During the follow-up year, 40% of patients with reference eosinophil counts, 42% with elevated counts, and 43% with low counts experienced ≥1 COPD exacerbations, while 16%, 18%, and 17%, respectively, experienced ≥2 COPD exacerbations. Patients with elevated blood eosinophil counts (8.9%) had an overall 13% higher exacerbations rate during the following year than patients in the reference group (87.7%) (Table). When investigating this association in different patient subgroups defined by patient characteristics, i.e. gender, smoking status, ICS use, and GOLD groups, we found a significant difference between ex-smokers and current smokers; with higher rate restricted to ex-smokers (Table). To investigate this further, we compared the exacerbation rates in four different patient subgroups defined by smoking status and eosinophil counts, the reference rate being that of ex-smokers with eosinophils in the reference range (0.05–0.45x10^9/L). Ex-smokers with elevated eosinophil counts had the highest exacerbation rate (RR 1.30; 1.14–1.48); and current smokers with elevated eosinophil counts had the lowest exacerbation rate (RR 0.89; 0.73–1.08). We also found significant associations between elevated eosinophil counts and exacerbation rates in men

(RR 1.21; 1.06–1.38), patients treated with ICS (RR 1.17; 1.02–1.35), and patients with GOLD group B (Table). However, no significant effect modification occurred by any of these characteristics (Table). As the observed increased exacerbation rate with elevated blood eosinophil counts was restricted to ex-smokers, we further studied associations within this subgroup. A significant increased exacerbations rate with elevated eosinophil counts was observed in male ex-smokers (n=2,914; RR 1.40; 1.20–1.64), ex-smokers treated with ICS (n=2,545; RR 1.37; 1.17–1.62) and ex-smokers with GOLD groups B-D. However, no significant effect modification occurred by these characteristics. For COPD patients with low eosinophil counts (3.4%), the exacerbation rate was not significantly different from that of patients with reference counts (RR 1.06; 0.89–1.27).

Table: Rate Ratios (95% CI) of the association between elevated blood eosinophil count and COPD exacerbations during the follow-up year in the total population of patients with COPD and in subgroups of patients defined by gender, smoking status, ICS therapy and GOLD groups.

Study population and subgroups	Patients with COPD (*n=8,318*)				
	Prevalence of elevated eosinophil counts (%)	RR* (95% CI)	*P* value	N	*P-value interaction*
Total population of patients with COPD	8.9	**1.13 (1.01-1.26)**	**0.03**	8,318	
Male patients n=4,695 (56.4%)	11.6	**1.21 (1.06-1.38)**	**0.005**	4,695	0.11
Female patients n=3,623 (43.6%)	5.5	0.98 (0.80-1.21)	0.88	3,623	
Current smokers n=3,610 (43.4%)	8.7	0.86 (0.71-1.05)	0.14	3,610	**0.0002**
Ex-smokers n=4,708 (56.6%)	9.1	**1.32 (1.15-1.51)**	**<0.0001**	4,708	
Patients on ICS‡ n=4082 (49.1%)	9.4	**1.17 (1.02-1.35)**	**0.03**	4,082	0.29
Patients not on ICS n=4236 (50.9%)	8.5	1.02 (0.84-1.24)	0.82	4.236	
GOLD groups§ Data available n=6,660 (80%)				6,600	
GOLD A n=2,357 (35.4%)	8.2	0.99 (0.77-1.29)	0.97	2,357	reference
GOLD B n=1,364 (20.5%)	8.8	**1.33 (1.02-1.73)**	**0.04**	1,364	0.07
GOLD C n=1,379 (20.7%)	7.9	1.27 (0.99-1.63**)**	0.06	1,379	0.12
GOLD D n=1,560 (23.4%)	9.6	1.17 (0.95-1.44)	0.13	1,560	0.24

Legend: The table shows the rate of COPD exacerbations in patients with elevated eosinophil counts (≥0.45x10^9/L) relative to patients with reference eosinophil counts (0.05 to <0.45x10^9/L) in each subgroup shown in column one. Differences between subgroups were tested by including an interaction term of elevated eosinophil count and the variable used to define the categories of the subgroup in a multiple regression model (e.g. interaction term of elevated eosinophil count (yes/no)*gender (male/female) had a P-value of 0.11)

Abbreviations: FEV_1 = forced expiratory volume in 1 sec; FVC = forced vital capacity; ICS = inhaled corticosteroids; GOLD = Global initiative for chronic Obstructive Lung Disease; MRC = Medical Research Council

*Rate Ratio adjusted for potential confounders

‡Maintenance treatment with inhaled corticosteroids.

§GOLD groups for patients with FEV_1/FVC <0.70, defined based on MRC score ≥2 (yes, B or D; no, A or C), number of baseline exacerbations ≥2 or leading to hospitalization ≥1 or FEV_1% predicted <50% (yes, C or D; no, A or B). Obstruction defined as FEV_1/FVC <0.70 at spirometry measurement closest to index date within ≤5 years.

We show that elevated blood eosinophil count when COPD was stable (>0.45x10^9/L) is associated with a higher rate of having an exacerbation in the following year. We observed the following: (i) the increased exacerbations rate with elevated eosinophil count was restricted to ex-smokers; (ii) this association was significant in male ex-smokers and was also found in patients on ICS; (iii) patients with elevated eosinophil count who were currently smoking showed the lowest exacerbations rate; and, (iv) there was no association between low eosinophil counts and COPD exacerbations.

A recent observational study [9] reported that blood eosinophil counts >0.34x10^9/L are associated with increased risk of both moderate and severe exacerbations in 7,225 patients with spirometrically confirmed COPD in the general population. However, this study did not investigate other patient characteristics that may potentially affect the association between blood eosinophils and exacerbations [9]. Our findings suggest that elevated blood eosinophil counts present in ex-smokers during stable COPD may identify patients with an increased susceptibility to exacerbations in the near future. These patients may constitute a target population for more specific treatment of their eosinophilic inflammation, since the increased risk was more pronounced in patients receiving ICS and ICS does not appear to lower the blood eosinophil count [10]. Our finding of a higher percentage of men than women having elevated eosinophil counts is consistent with the Copenhagen study [9]. Gender-related differences in dimension, structure, and function of the airways, together with variations in pathophysiologic and more specifically inflammatory mechanisms elicited by tobacco smoking, may lead to differences in clinical manifestations of airway disease [11-13]. There is also some evidence that active tobacco smoking has a suppressive effect on eosinophils and inflammatory cells or cytokines [14], even in intermittent smokers [15].

We acknowledge that our study population was broader than the “classical COPD population” included in clinical trials. Real-life patients include a diverse spectrum of individuals with a physician’s diagnosis of COPD. Many of these patients would not meet

eligibility criteria for randomized controlled trials [16,17], but are representative of the diverse patients seen by clinicians. Study strengths include the large patient population drawn from geographically and socioeconomically diverse practices throughout the UK. In addition, 85% of patients had recent spirometry results and GOLD groups A–D was calculated in 80% of patients. There are, however, some study limitations. Full blood count measurements are part of routine practice in COPD management and were available in 81% of our cohort. Although we used eosinophil counts at stable disease, we cannot exclude that specific indications may have influenced blood eosinophil levels, thereby underestimating associations between eosinophils and exacerbations. Moreover, we studied only the association with exacerbation rate in the subsequent year and did not assess whether there is a sustained increased risk over time. Furthermore, we used the mMRC dyspnea scale score to assign GOLD groups A–D, however results may have been different had we used the COPD assessment test [18].

To conclude, we show that elevated blood eosinophil counts may predict COPD exacerbation risk in some patient subgroups. This analytical strategy may eventually help in targeting therapy to specific patients, so benefit is maximized and risk minimized for individual patients.

References

1. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, Haldar P, McCormick M, Haldar K, Kebadze T, Duvoix A, Lindblad K, Patel H, Rugman P, Dodson P, Jenkins M, Saunders M, Newbold P, Green RH, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662-671.

2. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, Lomas DA, Barer MR, Johnston SL, Pavord ID, Brightling CE. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. *Am J Respir Crit Care Med* 2012; 186: 48-55.

3. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *Lancet Respir Med* 2015; 3: 435-*442.

4. Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, Vogelmeier C, Fabbri LM, Chanez P, Dahl R, Disse B, Finnigan H, Calverley PM. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. *Lancet Respir Med* 2016; 4: 390-398.

5. Optimum Patient Care. OPCRD. http://optimumpatientcare.org/opcrd/.

6. UK National Health Service (NHS). Full Blood Count. http://www.pathology.leedsth.nhs.uk/pathology/ClinicalInfo/Haematology/FullBloodCount.aspx.

7. Ver Hoef JM, Boveng PL. Quasi-Poisson vs. negative binomial regression: how should we model overdispersed count data? *Ecology* 2007; 88: 2766-2772.

8. Global initiative for chronic obstructive lung disease (GOLD). Global Strategy for the Diagnosis, management and prevention of COPD. 2016.

9. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG. Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. *Am J Respir Crit Care Med* 2016; 193: 965-974.

10. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J* 2016; 47: 1374-1382.

11. Becklake MR, Kauffmann F. Gender differences in airway behaviour over the human life span. *Thorax* 1999; 54: 1119-1138.

12. Faner R, Gonzalez N, Cruz T, Kalko SG, Agusti A. Systemic inflammatory response to smoking in chronic obstructive pulmonary disease: evidence of a gender effect. *PLoS One* 2014; 9: e97491.

13. Aryal S, Diaz-Guzman E, Mannino DM. Influence of sex on chronic obstructive pulmonary disease risk and treatment outcomes. *Int J Chron Obstruct Pulmon Dis* 2014; 9: 1145-1154.

14. van d, V, Postma DS, Timens W, ten Hacken NH. Acute effects of cigarette smoke on inflammation and oxidative stress: a review. *Thorax* 2004; 59: 713-721.

15. van d, V, Postma DS, Timens W, Hylkema MN, Willemse BW, Boezen HM, Vonk JM, de Reus DM, Kauffman HF, ten Hacken NH. Acute effects of cigarette smoking on inflammation in healthy intermittent smokers. *Respir Res* 2005; 6: 22.

16. Travers J, Marsh S, Caldwell B, Williams M, Aldington S, Weatherall M, Shirtcliffe P, Beasley R. External validity of randomized controlled trials in COPD. *Respir Med* 2007; 101: 1313-1320.

17. Halpin DM, Kerkhof M, Soriano JB, Mikkelsen H, Price DB. Eligibility of real-life patients with COPD for inclusion in trials of inhaled long-acting bronchodilator therapy. *Respir Res* 2016; 17: 120.

18. Karloh M, Fleig MA, Maurici R, Pizzichini MM, Jones PW, Pizzichini E. The COPD Assessment Test: What Do We Know So Far?: A Systematic Review and Meta-Analysis About Clinical Outcomes Prediction and Classification of Patients Into GOLD Stages. *Chest* 2016; 149: 413-425.