A new piece in the puzzle: the eosinophil and the development of COPD

Nayia Petousi [1,2], Abigail Wooden[3] and Richard E.K. Russell [1,2]

[1]Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK. [2]Oxford Centre for Respiratory Medicine, Oxford University Hospitals, Oxford, UK. [3]Southampton University Hospital, Southampton, UK.

Corresponding author: Richard E.K. Russell (richard.russell@ndm.ox.ac.uk)

Shareable abstract (@ERSpublications)
A large prospective population study has clearly demonstrated that blood eosinophils predict the development of airflow obstruction. This insight leads to the potential for early targeted intervention to prevent this happening. https://bit.ly/3vk7mBu

Cite this article as: Petousi N, Wooden A, Russell REK. A new piece in the puzzle: the eosinophil and the development of COPD. *Eur Respir J* 2021; 58: 2101105 [DOI: 10.1183/13993003.01105-2021].

Received: 16 April 2021
Accepted: 21 April 2021

COPD is associated with high morbidity and mortality worldwide, with overall high personal, societal and economic impact [1].

While the definition and diagnosis of COPD relies on demonstrating obstructive spirometry, it is widely recognised that COPD in later adult life is the result of several different lung function decline trajectories [2], and also that disease profiles, *e.g.* symptomatology or exacerbation rates, vary significantly between patients, irrespective of the degree of airflow obstruction [3]. This heterogeneity, as well as the complex poorly understood pathogenesis in COPD [4], poses significant challenges to the effective management of COPD. Another challenge is that COPD is diagnosed late in the disease process when already significant irreversible lung damage has occurred, thus limiting the ability of interventions to modify its trajectory and outcome.

As such, experts in the field are shifting their focus on improving disease phenotyping and stratification and on searching for "treatable traits" and "relevant biomarkers" so as to improve diagnosis, treatment and ultimately patient outcomes, and provide a personalised approach for our patients [5].

This search has led to the recognition that the peripheral blood eosinophil count is an important, reliable, easy-to-measure and clinically relevant biomarker in COPD, particularly in relation to exacerbation risk [6]. It has demonstrable value in predicting response to treatments that target airway eosinophilic inflammation in COPD, such as inhaled or systemic corticosteroids in a variety clinical scenarios [7–9], or more recently biologics [10, 11]. Indeed, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) has introduced the blood eosinophil count as a biomarker for estimating the efficacy of inhaled corticosteroids (ICS) for the prevention of exacerbations: the 2020 GOLD strategy for pharmacological therapies in COPD advocate the use of ICS in patients with a peripheral blood eosinophil count of >300 cells·μL^{-1} or with >100 cells·μL^{-1} in patients who experience exacerbations despite long-acting muscarinic antagonist/long-acting beta agonist treatment [12]. This has been further supported by the publication of recent American Thoracic Society clinical practice guidance for the pharmacological treatment of COPD [13].

Several cross-sectional studies have found an association between blood eosinophil count and the presence of COPD or reduced lung function [14–16]. However, there is little work done or evidence for the role of blood eosinophil count as a biomarker that may predict the development of COPD or one that is associated with progressive lung function decline.

In this issue of the *European Respiratory Journal*, Park *et al.* [17] conducted a large longitudinal study of men and women without COPD or evidence of obstructive lung function on spirometry at baseline, and demonstrated that a higher blood eosinophil count was associated with the risk of developing obstructive

lung disease (OLD). Specifically, they followed-up 359 456 relatively young Korean adults with no history of asthma or evidence of obstructive lung function at baseline and found that over a median of 5.6 years, 5008 participants developed OLD (2.1 per 1000 persons-years incidence rate), defined as pre-bronchodilator forced expiratory volume in 1 s (FEV_1) to forced vital capacity ratio <0.7 and FEV_1 <80% predicted. They found that individuals with blood eosinophil count >500 cells·μL^{-1} had almost a two-fold risk of developing OLD (hazard ratio (HR) was 1.72 (95% CI 1.51–1.95) compared to those with <100 cells·μL^{-1}). Although their analysis used categories of eosinophil values, *e.g.* <100, 100–200, 200–300, 300–400, >500, they showed a "dose–response" relationship between blood eosinophil count and risk of developing OLD, with the HR being >1.30 if the eosinophil count was >200 cells·μL^{-1}.

One important aspect of this study is that it excluded patients with a history of asthma, often considered a confounder as eosinophilic inflammation is common in asthma. This study also has demonstrated that the increased risk of OLD development associated with the blood eosinophil count is independent of smoking status (never, former or current), although the dose–response relationship suggests increased risk for incident OLD at lower eosinophil counts for current smokers. This finding hints at the potential for a, thus far, unrecognised mechanism for these eosinophil-related changes.

It is worth acknowledging another significant finding from this study which helps answer a frequently asked question: is the blood eosinophil count a stable phenotype? This large longitudinal study clearly demonstrated that those with low eosinophil counts tend to stay low, those who are high stay high, and there are some in-between who tend to oscillate. The blood eosinophil count can therefore be considered to be stable and is certainly comparable with other biological variables used in clinical practice.

A limitation of the study is that spirometric measurements are all pre-bronchodilator (as they were part of a health surveillance programme), and as such OLD cannot be equated to COPD, as the definition of COPD requires post-bronchodilator measurements. Another limitation is that the authors do not display a relationship between rate of lung function decline and blood eosinophil count, which would have been helpful to observe. This was due in part to the relatively short follow-up in this study; given the natural history of the development of COPD, longer term follow up will answer this question.

Yet, this is the first prospective longitudinal study of this size that assessed and found a positive association of the blood eosinophil count with the development of OLD in healthy young individuals. Its findings are significant and important and have the potential to alter thinking and practice in the field.

With the exception of smoking (and possibly alpha-1 antitrypsin deficiency), little progress has been made in identifying other modifiable traits that increase an individual's risk of developing COPD, or for having rapid lung function decline once diagnosed with COPD. This is an important consideration given that <30% of smokers develop COPD and that non-smoking COPD is recognised as a major subgroup [18]. The peripheral blood eosinophil count is not only an easily obtainable and commonly measured parameter, but importantly it is biomarker associated with treatment response and thus could be considered as "treatable". This study has added a new dimension to the role of eosinophils in COPD: further understanding risk.

Thus, a question to consider is whether the peripheral blood eosinophil count should be part of screening (alongside spirometry) for COPD, *e.g.* in healthy young to middle-aged people with a smoking history. Can the risk demonstrated for disease development and progression be modified? Should an elevated blood eosinophil count in the presence of obstructive spirometry should be a prompt to consider initiation of ICS, even in the absence of symptoms or exacerbation history, in an attempt to slow down further progression in lung function decline? Whilst there is no strong evidence for the latter, the current study by Park *et al.* [17], as well as previous studies by Barnes *et al.* [19] and Hancox *et al.* [20] would support this approach.

A fundamental question is whether the blood eosinophil count can be used as a "predictor of developing chronic airways disease" in the efforts of the community for *early detection* of airway disease that would allow a *meaningful intervention*, *i.e.* one that could modify the natural history of the disease, preventing or slowing down the development of COPD. The authors of the current study suggest in their discussion that "individuals with higher eosinophil counts may benefit from closer monitoring of lung function in order to facilitate early detection and intervention of OLD". Whilst a laudable goal this is problematic and impractical for two reasons. First, only a very small proportion of people will develop COPD, with a predicted incidence rate of <4 per 1000 person-years, even in those a blood eosinophil count of >500 cells·μL^{-1} (from their current study). Second, the current available tool for monitoring lung function, spirometry, is crude, slow to change and predominantly reflects changes in the larger airways. As a result,

considerable disease may be accumulating over time in the smaller airways of the lung before a detectable change in FEV_1 can be observed, missing the opportunity for true early preventative intervention [21, 22].

What is desirable, and potentially possible, would be to utilise the blood eosinophil count, in those individuals with high blood eosinophil count who may already have subclinical airway inflammation or disease and who are likely to develop airway flow limitation in the future, for targeted monitoring or even intervention. To fully exploit this potential gain, we will require new measures of disease activity and function in the lung, beyond spirometry. These should be sensitive to subtle changes in airway pathology, particularly in the small airways. This presents an opportunity for future research to exploit novel methodologies in measuring lung disease with sensitive physiological endpoints [23]. The new knowledge presented by PARK *et al.* [17] enables a new focus on: identifying early airways disease in individuals with high eosinophil counts (even in the absence of obstructive spirometry); assessing whether this is modifiable with treatment that targets eosinophilic inflammation; and also to investigate with targeted longitudinal cohorts whether this progresses to COPD.

Finally, there is clearly a lot we do not understand about this "complex cell". The mechanisms which underpin the irrefutable epidemiological and clinical data on the involvement of the eosinophil are poorly understood. Historically these cells were associated with allergic disease and asthma, but this is clearly not the case from this study and others. The patients studied in the work by PARK *et al.* [17] have COPD and the ones with higher levels of eosinophils are indistinguishable from those without [17]. There are many fundamental questions that remain as to why some subjects have higher blood levels than others, leading to clinical phenotypes, and if the eosinophil is a marker or effector in this. An association is not causality. This current study is another piece in the puzzle but also raises more questions. The answers will hopefully lead to a more precise approach to the diagnosis, prognostication and treatment of COPD.

Conflict of interest: None declared.

Support statement: N. Petousi and R.E.K. Russell are supported by the National Institute for Health Research (NIHR) Oxford Biomedical Research Centre (BRC).

References

1 Vos T, Lim SS, Abbafati C, *et al.* Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396: 1204–1222.
2 Lange P, Celli B, Agusti A, *et al.* Lung-function trajectories leading to chronic obstructive pulmonary disease. *N Engl J Med* 2015; 373: 111–122.
3 Turner AM, Tamasi L, Schleich F, *et al.* Clinically relevant subgroups in COPD and asthma. *Eur Respir Rev* 2015; 24: 283–298.
4 Barnes PJ. Inflammatory endotypes in COPD. *Allergy* 2019; 74: 1249–1256.
5 August A, Bel E, Thomas M, *et al.* Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; 47: 410–419.
6 David B, Bafadhel M, Koenderman L, *et al.* Eosinophilic inflammation in COPD: from an inflammatory marker to a treatable trait. *Thorax* 2021; 76: 188–195.
7 Bafadhel M, McKenna S, Terry S, *et al.* 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.
8 Bafadhel M, Peterson S, De Blas MA, *et al.* Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. *Lancet Respir Med* 2018; 6: 117–126.
9 Vedel-Krogh S, Nielsen SF, Lange P, *et al.* 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 Pavord ID, Chanez P, Criner GJ, *et al.* Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med* 2017; 377: 1613–1629.
11 Criner GJ, Celli BR, Brightling CE, *et al.* Benralizumab for the prevention of COPD exacerbations. *N Engl J Med* 2019; 381: 1023–1034.
12 Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease. 2020 Report. https://goldcopd.org/wp-content/uploads/2019/12/GOLD-2020-FINAL-ver1.2-03Dec19_WMV.pdf
13 Nici L, Mammen MJ, Charbek E, *et al.* Pharmacologic management of COPD: an official ATS clinical practice guideline. *Am J Respir Crit Care Med* 2020; 201: e56–e69.

14 Kolsum U, Southworth T, Jackson N, *et al.* Blood eosinophil counts in COPD patients compared to controls. *Eur Respir J* 2019; 54: 1900633.

15 Mogensen I, Vonk JM, Wijnant SRA, *et al.* Blood eosinophil level and lung function trajectories: cross-sectional and longitudinal studies in European cohorts. *ERJ Open Res* 2020; 6: 00320-2020.

16 Saha S, Brightling CE. Eosinophilic airway inflammation in COPD. *Int J Chron Obstruct Pulmon Dis* 2006; 1: 39–47.

17 Park HY, Chang Y, Kang D, *et al.* Blood eosinophil counts and the development of obstructive lung disease: the Kangbuk Samsung Health Study. *Eur Respir J* 2021; 58: 2003823.

18 Lamprecht B, McBurnie MA, Vollmer WM, *et al.* COPD in never smokers: results from the population-based burden of obstructive lung disease study. *Chest* 2011; 139: 752–763.

19 Barnes NC, Sharma R, Lettis S, *et al.* Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. *Eur Respir J* 2016; 47: 1374–1382.

20 Hancox RJ, Pavord ID, Sears MR. Associations between blood eosinophils and decline in lung function among adults with and without asthma. *Eur Respir J* 2018; 51: 1702536.

21 Hogg JC, Pare PD, Hackett TL. The contribution of small airway obstruction to the pathogenesis of chronic obstructive pulmonary disease. *Physiol Rev*. 2017; 97: 529–552.

22 Woodruff PG, Barr RG, Bleecker E, *et al.* Clinical significance of symptoms in smokers with preserved pulmonary function. *N Engl J Med* 2016; 374: 1811–1821.

23 Petousi N, Talbot NP, Pavord ID, *et al.* Measuring lung function in airways diseases: current and emerging techniques. *Thorax* 2019; 74: 797–805.