Peripheral eosinophil count as a biomarker for the management of COPD: not there yet

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Chronic obstructive pulmonary disease (COPD) is associated with acute and chronic pulmonary as well as systemic inflammation [1]. Anti-inflammatory treatments, such as inhaled corticosteroids (ICS) and oral roflumilast, are recommended for COPD patients [2]. These drugs are effective agents for the prevention of COPD exacerbations and improvement of lung function and have various effects on health status, but they are associated with adverse events, the most concerning being pneumonia (ICS) and diarrhoea (roflumilast).

It has been recognised for many years that some patients with COPD have eosinophilic airway inflammation both in a stable state [3] and during exacerbations [4]. More recently, the Copenhagen City Lung study strongly suggested that a high peripheral blood eosinophil count (>340 cells per µL) was associated with an increased risk of severe COPD exacerbations [5]. In contrast, and similar to the results of the ECLIPSE study [6] and of Zysman *et al.* [7], both of which were conducted in patients with COPD, no increased risk of moderate-severe exacerbations was found when a threshold of 2% blood eosinophils was used [5]. Finally, contributing to the overall confusion about the role of eosinophils as a risk factor for COPD outcomes, increased blood eosinophils in patients with COPD were also associated with better lung function, improved quality of life [6, 8], and even reduced mortality [9]. However, eosinopenia (counts of $<0.05\times10^9$ per L) seemed to be associated with an increased risk of sepsis [10], worse outcomes in patients presenting to hospital with an acute exacerbation of COPD [11, 12], and an increased risk of pneumonia [13].

Interestingly, the subgroups of severe COPD patients who improve after taking oral steroids have eosinophilic airway inflammation, unlike the majority who do not respond to oral steroids [14]. Several *post hoc* analyses of recent randomised clinical trials have clearly shown that the effect of combination therapy with inhaled long-acting β-adrenoceptor agonists (LABA) and ICS [15, 16] or triple therapy [17, 18] is significantly increased in COPD patients with high blood eosinophil counts at baseline. One prominent exception to these findings is the FLAME (Effect of Indacaterol Glycopyronium *vs* Fluticasone

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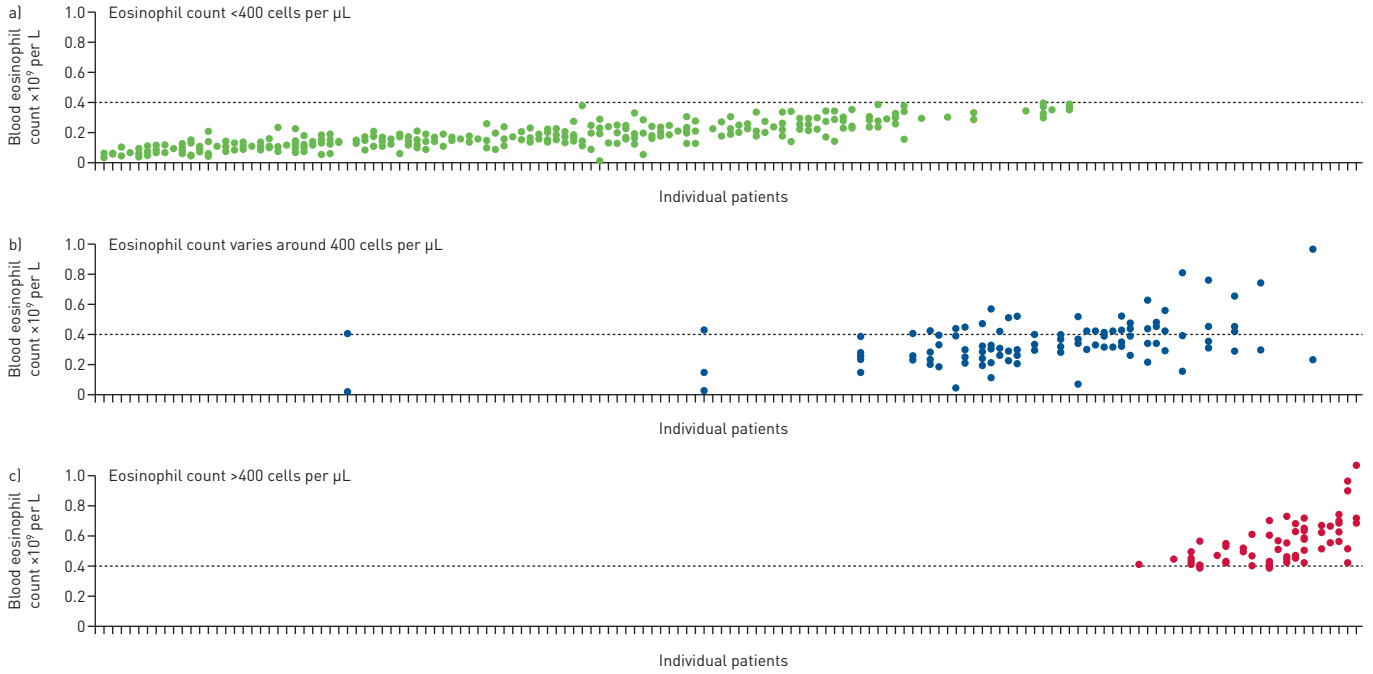

FIGURE 1 Repeated peripheral blood eosinophil counts during stable disease over 12 months in patients with chronic obstructive pulmonary disease (COPD). Individual patients with COPD are shown along the horizontal axis. a) Data for patients with eosinophil counts that were consistently <400 cells per µL (55%). b) Data for patients with eosinophil counts that varied around 400 cells per µL (35%). c) Patients with eosinophil counts that were consistently above 400 cells per µL (10%). Data from [29, 30]. The horizontal line at 400 cells per µL is defined as peripheral eosinophilia. Reproduced from [22] with permission from the publisher.

Salmeterol on COPD Exacerbations) study [19], which showed in a prospective pre-specified analysis and in a *post hoc* analysis including exacerbations [20] no difference in effect on exacerbations between patients treated with the LABA (indacaterol)/long-acting muscarinic antagonist (LAMA) (glycopyrronium) combination or the LABA (salmeterol)/ICS (fluticasone proprionate) arm and high blood eosinophil counts. A targeted anti-eosinophil therapy with the anti-interleukin-5 monoclonal antibody mepolizumab also seems to be more effective in the minority of eosinophilic COPD patients with blood eosinophil counts of >300 cells per µL at baseline [21].

These recent observations have heightened interest in peripheral eosinophil counts as a risk factor for COPD exacerbations and/or a predictor of response to ICS in clinical practice among the scientific and clinical communities and pharmaceutical industry [22]. So far, the major concerns about using blood eosinophils as biomarkers are threefold: 1) *post hoc* analyses of clinical trials suggest their use is based on single pre-trial measurements; 2) the threshold values, particularly the 2% cut-off, are well within the normal range; and 3) blood eosinophil counts have low reproducibility in COPD patients [6, 23].

In this issue of the *European Respiratory Journal*, Casanova *et al.* [24] examined the prevalence and stability of increased levels of blood eosinophils (⩾300 cells per µL) and their relationship to clinical exacerbations and survival in COPD patients and smokers without COPD who had had at least three blood eosinophil measurements over 1.5 years to >10 years of follow-up. In both COPD patients and smokers without COPD, they found that only 15% had stable eosinophilia with >300 cells per µL, almost 50% had eosinophil counts that oscillated above and below the 300 cells per µL threshold, and about 35% of subjects had persistent eosinophil counts of <300 cells per µL. They also found that a blood eosinophil count of ⩾300 cells per µL persisting over 2 years was not a risk factor for COPD exacerbations, but rather was associated with better survival.

The study by Casanova *et al.* [24] has strengths and weaknesses, which are properly addressed by the authors. In our opinion, the most notable strength is that the study is much closer to the real world than to a randomised clinical trial, and the most important weaknesses are that 1) different populations were studied; 2) blood eosinophils were measured at different intervals in different laboratories; and 3) the duration of follow-up was very broad, ranging from ~17 to >130 months.

Nonetheless, the message is quite clear: a "clinically relevant" high count of blood eosinophils (>300 cells per µL) is not reproducible in almost 50% of COPD patients, and this low reproducibility does not

improve if one selects 150 or >350 cells per μL. These results confirm the instability of high blood eosinophil counts over time, both in COPD cohorts [8, 25] and in the general population [23], as well as the survival advantage of patients with COPD who have persistently high eosinophil counts [9]. The study by Casanova *et al.* [24], however, does not confirm the increased risk of COPD exacerbations associated with high blood eosinophil counts or the excessive risk of pneumonia or mortality associated with low blood eosinophil counts.

At present, the optimal threshold for separation of high and low blood eosinophil count for use as a biomarker has not been established, nor has the best way of expressing it (absolute *versus* percentage). The most commonly proposed cut-off points have been a blood eosinophil count above and below 2% of the total white blood cell count or an absolute eosinophil count of 150–400 cells per μL, which is within the normal range (0–6% or 30–350 cells per μL) [26]. Others suggest that a more reliable threshold would be 4% or >400 cells per μL [27]. No prospective data regarding the sensitivity and specificity of these values in different populations with different *a priori* exacerbation risks are available. In contrast, some recent *post hoc* analyses of severe COPD patients with high eosinophil counts (4% or >300–400 cells per μL), notably in combination with a history of frequent exacerbations, suggest that these patients might be at increased risk of re-exacerbations/hospitalisation if ICS are withdrawn [27, 28]. However, only a small minority (~10%) of COPD patients have stable counts of >400 cells per μL (figure 1) [22].

While the community eagerly awaits properly designed and powered randomised trials, based on the results of the study by Casanova *et al.* [24] and other available data we suggest the following: 1) at the present time, blood eosinophil counts cannot be recommended as biomarkers for the management of individual patients with COPD, particularly because of their poor reproducibility over time; 2) ICS probably should be maintained and not withdrawn in patients with high blood eosinophil counts and a history of frequent exacerbations, irrespective of powerful bronchodilator combinations; and 3) ICS should be used with caution in COPD patients with persistent eosinopenia, and, if given, they should be carefully monitored for the increased risk of pneumonia.

References

1 Rabe KF, Watz H. Chronic obstructive pulmonary disease. *Lancet* 2017; 389: 1931–1940.
2 Vogelmeier CF, Criner GJ, Martinez FJ, *et al.* Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. *Eur Respir J* 2017; 49: 1700214.
3 Lacoste JY, Bousquet J, Chanez P, *et al.* Eosinophilic and neutrophilic inflammation in asthma, chronic bronchitis, and chronic obstructive pulmonary disease. *J Allergy Clin Immunol* 1993; 92: 537–548.
4 Saetta M, Di Stefano A, Maestrelli P, *et al.* Airway eosinophilia in chronic bronchitis during exacerbations. *Am J Respir Crit Care Med* 1994; 150: 1646–1652.
5 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.
6 Singh D, Kolsum U, Brightling CE, *et al.* Eosinophilic inflammation in COPD: prevalence and clinical characteristics. *Eur Respir J* 2014; 44: 1697–1700.
7 Zysman M, Deslee G, Caillaud D, *et al.* Relationship between blood eosinophils, clinical characteristics, and mortality in patients with COPD. *Int J Chron Obstruct Pulmon Dis* 2017; 12: 1819–1824.
8 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.
9 Suzuki M, Makita H, Konno S, *et al.* Asthma-like features and clinical course of chronic obstructive pulmonary disease. An analysis from the Hokkaido COPD cohort study. *Am J Respir Crit Care Med* 2016; 194: 1358–1365.
10 Shaaban H, Daniel S, Sison R, *et al.* Eosinopenia: is it a good marker of sepsis in comparison to procalcitonin and C-reactive protein levels for patients admitted to a critical care unit in an urban hospital? *J Crit Care* 2010; 25: 570–575.
11 Holland M, Alkhalil M, Chandromouli S, *et al.* Eosinopenia as a marker of mortality and length of stay in patients admitted with exacerbations of chronic obstructive pulmonary disease. *Respirology* 2010; 15: 165–167.
12 Steer J, Gibson J, Bourke SC. The DECAF score: predicting hospital mortality in exacerbations of chronic obstructive pulmonary disease. *Thorax* 2012; 67: 970–976.
13 Pavord ID, Lettis S, Anzueto A, *et al.* Blood eosinophil count and pneumonia risk in patients with chronic obstructive pulmonary disease: a patient-level meta-analysis. *Lancet Respir Med* 2016; 4: 731–741.
14 Chanez P, Vignola AM, O'Shaugnessy T, *et al.* Corticosteroid reversibility in COPD is related to features of asthma. *Am J Respir Crit Care Med* 1997; 155: 1529–1534.
15 Pascoe S, Locantore N, Dransfield MT, *et al.* 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.
16 Siddiqui SH, Guasconi A, Vestbo J, *et al.* Blood eosinophils: a biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2015; 192: 523–525.
17 Singh D, Papi A, Corradi M, *et al.* Single inhaler triple therapy *versus* inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2016; 388: 963–973.
18 Vestbo J, Papi A, Corradi M, *et al.* Single inhaler extrafine triple therapy *versus* long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. *Lancet* 2017; 389: 1919–1929.

19 Roche N, Chapman KR, Vogelmeier CF, *et al.* Blood eosinophils and response to maintenance chronic obstructive pulmonary disease treatment. Data from the FLAME trial. *Am J Respir Crit Care Med* 2017; 195: 1189–1197.
20 Papi A, Kostikas K, Wedzicha JA, *et al.* Dual bronchodilation response by exacerbation history and eosinophilia in the FLAME study. *Am J Respir Crit Care Med* 2017; in press [https://doi.org/10.1164/rccm.201709-1822LE].
21 Pavord ID, Chanez P, Criner GJ, *et al.* Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med* 2017; 377: 1613–1629.
22 Bafadhel M, Pavord ID, Russell REK. Eosinophils in COPD: just another biomarker? *Lancet Respir Med* 2017; 5: 747–759.
23 Oshagbemi OA, Burden AM, Braeken DCW, *et al.* Stability of blood eosinophils in patients with chronic obstructive pulmonary disease and in control subjects, and the impact of sex, age, smoking, and baseline counts. *Am J Respir Crit Care Med* 2017; 195: 1402–1404.
24 Casanova C, Celli BR, de-Torres JP, *et al.* Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. *Eur Respir J* 2017; 50: 1701162.
25 Hamad GA, Cheung W, Morice A, *et al.* Eosinophils in COPD: how many swallows make a summer? *Eur Respir J* 2018; in press [https://doi.org/10.1183/13993003.02177-2017].
26 Liess BD, Staros EB. Eosinophils. https://emedicine.medscape.com/article/2090595-overview Date last accessed: October 16, 2017. Date last updated: March 28, 2014.
27 Calverley PMA, Tetzlaff K, Vogelmeier C, *et al.* Eosinophilia, frequent exacerbations, and steroid response in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2017; 196: 1219–1221.
28 Watz H, Tetzlaff K, Wouters EF, *et al.* 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.
29 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.
30 Bafadhel M, McKenna S, Terry S, *et al.* Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. *Am J Respir Crit Care Med* 2011; 184: 662–671.