Journal of Pulmonology and Respiratory Diseases

González-Aguirre and Álvarez-Martínez, J Pulm Res Dis 2017, 1:1

Editorial Open Access

Eosinophilic Inflammation: A Critical Piece of the Chronic Obstructive Pulmonary Disease Puzzle

Julio E González-Aguirre* **and Natalia Álvarez-Martínez**

Department of Pulmonary and Critical Care Medicine, Nuevo León Autonomous University, Mexico

***Corresponding author:** Julio Edgardo González-Aguirre, Department of Pulmonary and Critical Care Medicine, Nuevo León Autonomous University, Av. Francisco I. Madero 1500, Suburb: Mitras Centro, Monterrey, N.L. 64460, México, Tel: (01)-81-8333-8381; E-mail: jeglza111@gmail.com

Received date: November 05, 2017; **Accepted date:** November 06, 2017; **Published date:** November 10, 2017

In the last ten years, the publication of more than 2,300 COPD-related randomized controlled trials (RCT) has shown us valuable lessons. The individualization of the therapeutic approach based on the analysis of the intensity of the symptoms and the frequency of the exacerbations constitute one of the leading characteristics of the modern treatment of the Chronic Obstructive Pulmonary Disease (COPD). However, even patients who share characteristics that unite them within the same group (e.g., A, B, C, and D groups of Global Initiative for COPD) could present essential differences in the molecular pathways that lead to the development of the disease.

The pulmonary inflammation profile triggered by chronic exposure to tobacco smoke results in airway infiltration by neutrophils, alveolar macrophages, and lymphocytes [1]. Although eosinophilic infiltration was traditionally considered not being part of the inflammatory characterization of COPD, recent research has described a population of patients with "disproportionately" elevated count of eosinophils in the airway, sputum, or blood. Paradoxically, the current knowledge about the role of eosinophilic inflammation in COPD is scarce, although it seems to be present in a significant proportion of patients. In this regard, the most conservative studies report a frequency of eosinophilic inflammation in the order of 35% [2,3]; nonetheless, authors such as Iqbal et al. [4], Roche et al. [5] and Pascoe et al. [6] have found it in 52, 60.9 and 66% of the studied population, respectively.

Eosinophilic inflammation in COPD does not necessarily imply a marked rise in the eosinophils count. Given the inclusion of up to 40% of atopic patients in the healthy control population used by establishing reference laboratory values [7], it is very probable that our concept of eosinophil count normality implies a relatively high threshold to classify a patient as a carrier of eosinophilia. The exclusion of patients with atopy identified by clinical history or by elevation in the serum IgE of the control population resulted in a 20% decrease in the average standard value of eosinophils [8]. On the other hand, the biological material studied (blood or sputum) also has significant implications; although sputum analysis is a direct measure of the intensity of inflammation in the airway, eosinophils quantification in this material is technically challenging. Non-controlled factors during the induction, collection, and processing of the sputum sample can decrease the diagnostic performance [9]. These difficulties markedly contrast with the relative ease of the blood samples handling and processing. Finally, blood eosinophils also show a statistically significant and moderately robust correlation with eosinophil airway infiltration [10].

From a practical point of view, there are three clinical scenarios in which the quantification of eosinophils in blood could be potentially useful:

- **Prediction of adverse outcomes:** The available epidemiological evidence relates blood eosinophils count with some undesirable outcomes. The study of more than 7000 patients with COPD in the Copenhagen General Population Study showed an increase in the risk of severe acute exacerbation of COPD (AECOPD) in patients with more than 340 eosinophils/μL (multivariable-adjusted incidence rate ratios of 1.76 [95% CI, 1.56-1.99]) [11]. In this study, the absolute number of eosinophils had a higher power for AECOPD prediction compared to the count relative to total leukocytes. On the contrary, the evidence concerning the increase in mortality is less robust. In the general COPD population, increased risk of death was neither related to eosinophilia nor positive skin tests [12].
- **Treatment guide in patients with stable COPD:** Due to its capability to reduce the frequency of AECOPD, inhaled corticosteroids (IC) have a leading role in the treatment of COPD. Notwithstanding, its use is far from harmless given its relationship with several adverse effects (e.g., pneumonia, oral candidiasis, osteoporosis, etc.). With the intention to improve the cost-benefit ratio of the treatment, the elevated blood eosinophil count has been proposed as a tool to select those patients who could present more significant benefit with the use of IC. Unfortunately, this idea is based only on data obtained from retrospective and post-hoc studies designed with other primary objectives. A post-hoc analysis of the FLAME trial found that the combination of indacaterol and glycopyrronium is superior to the use of fluticasone plus salmeterol for the prevention of AECOPD, even in patients with blood eosinophils higher than 2% or 150 cells/μL [5]. IC therapy did not prove to be superior even after the selection of patients based on higher thresholds of eosinophils. The FLAME trial excluded patients with more than 600 cells/μL; however, these patients represented only 3.1% of the screened population, so the results of the FLAME study are applicable for the 96.9% remaining. In contrast, a post-hoc analysis of the Wisdom study showed a higher frequency of exacerbations after discontinuing IC in patients with blood eosinophils higher than 4% or 300 cells/uL, the rise in exacerbation frequency became more pronounced as the eosinophil cutoff level rose [13]. Though, a subsequent scrutiny showed that the increased risk was only statistically significant in patients who additionally had a history of at least two exacerbations in the previous 12 months [14]. To the best of our knowledge, there is still no evidence from controlled clinical trials specifically designed to prove that IC treatment in patients selected only for their blood eosinophils level results in better clinical

outcomes. This is in line with current GOLD initiative recommendations [15].

- **Treatment guide in patients with AECOPD:** During AECOP exists an increase in neutrophils, TNF alpha and IL6 in the airway [16], however, in approximately 45% of patients, there is an enhanced production of IL-5 and Chemokine (C-C motif) ligand 1 [17]. The rise of eosinophils in the blood could identify these Th-2 type exacerbations. Eosinophilic AECOP frequently occurs in patients with eosinophilia during stable disease (OR 9.16, p<0.001) [10]. Its occurrence confers a better prognosis; patients with eosinophils at admission >200 cells/μL exhibits less frequently positive sputum cultures [10] and also have a shorter hospital length of stay [18]. There is at least one placebo-controlled clinical trial designed to test the no inferiority of the AECOPD treatment guided by blood eosinophils count. In this study, Bafadhel M et al. randomized patients with eosinophils greater than 2% at hospital admission to receive placebo or prednisolone for 10 days. The main objectives were treatment failure and quality of life measured by the chronic respiratory questionnaire. Patients with eosinophilia showed greater improvement when they received systemic corticosteroids (mean difference, 0.45, 95% confidence interval, 0.01-0.90, p=0.04). In this population, treatment failure was lower with prednisolone (2 vs. 15%, p=0.04) [19]. These data match with the results of the post-hoc analysis of three clinical trials originally designed to compare systemic corticosteroids with placebo [20]. Finally, larger RCT should replicate these findings before their incorporation into daily clinical practice.

Inflammation mediated by Th2 cytokines is a specific COPD endotype. Eosinophilic inflammation could be only one of the various attributes of the disease that eventually will lead to the development of a well-established phenotype, for example, the asthma-COPD overlap syndrome. Treating the isolated eosinophilic trait may not be sufficient, in this regard, direct inhibition of IL-5 is not more effective than placebo for reducing the frequency of AECOPD [21]. Also, this hypothesis could explain why the mortality related to COPD is higher in patients with elevated eosinophils exclusively in the presence of concomitant asthma [22].

Could eosinophils be the link between COPD and asthma? The Th2-profile could be the joint between both diseases; besides, it supports at least some genetic coincidence between patients with asthma and COPD, who in clinical practice could meet the diagnostic criteria of the asthma-COPD overlap syndrome [23].

At this moment, eosinophilic inflammation remains as a critical piece of the complex puzzle of the optimal treatment of patients with COPD.

References

1. Hogg JC, Chu F, Utokaparch S, Woods R, Elliott WM, et al. (2004) The nature of small-airway obstruction in chronic obstructive pulmonary disease. N Engl J Med 350: 2645-2653.
2. Cheng SL, Lin CH (2016) Effectiveness using higher inhaled corticosteroid dosage in patients with COPD by different blood eosinophilic counts. Int J Chron Obstruct Pulmon Dis 11: 2341-2348.
3. Oshagbemi OA, Burden AM, Braeken DCW, Henskens Y, Wouters EFM, et al. (2017) 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 195: 1402-1404.
4. Iqbal A, Barnes NC, Brooks J (2015) Is Blood Eosinophil Count a Predictor of Response to Bronchodilators in Chronic Obstructive Pulmonary Disease? Results from Post Hoc Subgroup Analyses. Clin Drug Investig 35: 685-688.
5. Roche N, Chapman KR, Vogelmeier CF, Herth FJF, Thach C, et al. (2017) Blood Eosinophils and Response to Maintenance Chronic Obstructive Pulmonary Disease Treatment. Data from the FLAME Trial. Am J Respir Crit Care Med 195: 1189-1197.
6. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID (2015) 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 3: 435-442.
7. Britton J, Pavord I, Richards K, Knox A, Wisniewski A, et al. (1994) Factors influencing the occurrence of airway hyperreactivity in the general population: the importance of atopy and airway calibre. Eur Respir J 7: 881-887.
8. Beeh KM, Beier J, Kornmann O, Mander A, Buhl R (2003) Long-term repeatability of induced sputum cells and inflammatory markers in stable, moderately severe COPD. Chest 123: 778-783.
9. Bafadhel M, Pavord ID, Russell REK (2017) Eosinophils in COPD: just another biomarker? Lancet Respir Med 5: 747-759.
10. Kim VL, Coombs NA, Staples KJ, Ostridge KK, Williams NP, et al. (2017) Impact and associations of eosinophilic inflammation in COPD: analysis of the AERIS cohort. Eur Respir J 50: 1700853.
11. Vedel-Krogh S, Nielsen SF, Lange P, Vestbo J, Nordestgaard BG (2016) Blood Eosinophils and Exacerbations in Chronic Obstructive Pulmonary Disease. The Copenhagen General Population Study. Am J Respir Crit Care Med 193: 965-974.
12. Hospers JJ, Schouten JP, Weiss ST, Rijcken B, Postma DS (1999) Asthma attacks with eosinophilia predict mortality from chronic obstructive pulmonary disease in a general population sample. Am J Respir Crit Care Med 160: 1869-1874.
13. Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, et al. (2016) 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 4: 390-398.
14. Calverley PMA, Tetzlaff K, Vogelmeier C, Fabbri LM, Magnussen H, et al. (2017) Eosinophilia, Frequent Exacerbations, and Steroid Response in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med 196: 1219-1221.
15. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, et al. (2017) Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report: GOLD Executive Summary. Eur Respir J 22: 1750214.
16. Aaron SD, Vandemheen KL, Maltais F, Field SK, Sin DD, et al. (2013) TNFalpha antagonists for acute exacerbations of COPD: a randomised double-blind controlled trial. Thorax 68: 142-148.
17. Bafadhel M, McKenna S, Terry S, Mistry V, Reid C, et al. (2011) Acute exacerbations of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 184: 662-671.
18. Bafadhel M, Greening NJ, Harvey-Dunstan TC, Williams JE, Morgan MD, et al. (2016) Blood Eosinophils and Outcomes in Severe Hospitalized Exacerbations of COPD. Chest 150: 320-328.
19. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, et al. (2012) Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med 186: 48-55.
20. Bafadhel M, Davies L, Calverley PM, Aaron SD, Brightling CE, et al. (2014) Blood eosinophil guided prednisolone therapy for exacerbations of COPD: a further analysis. Eur Respir J 44: 789-791.
21. Brightling CE, Bleecker ER, Panettieri RA Jr., Bafadhel M, She D, et al. (2014) Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med 2: 891-901.

22. Diaz-Guzman E, Khosravi M, Mannino DM (2011) Asthma, chronic obstructive pulmonary disease, and mortality in the U.S. population. COPD 8: 400-407.

23. González-Aguirre JE, Mercado-Longoria R (2017) Asthma-COPD Overlap Syndrome: A work in Progress. Pulmonary and Critical Care Medicine 2: 1-2.