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

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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 infiltration 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/μL, 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, patients experience an increase in neutrophils, TNF alpha and ILs 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
