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Commentary

Blood Eosinophils Threshold and Clinical Outcome in COPD

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Chronic obstructive pulmonary disease (COPD) is a complex disorder characterized for pulmonary and systemic inflammatory implications which affects approximately 251 million people worldwide [1]. It is a major global burden predicted to be the third-leading cause of death by 2020. High quality research has been conducted to clarify the heterogeneity of disease and optimize treatment outcomes. Peripheral blood cell counts is a low cost and acessible tool with potential benefits in clinical practice [2]. Several studies suggested that blood eosinophil counts (and their proportions) could be a reliable marker to predict corticosteroid treatment responsiveness in COPD.

Eosinophils modulate innate and adaptive immunity through granule-derived proteins and cytokines, as well as direct cellular signaling. It is known for some time that eosinophils are actively implicated in inflammatory pathogenesis of COPD. Eosinophilic inflammation is a stable longitudinal phenotype in a substantial proportion of COPD [3] patients and there is reasonably good correlation between blood and airway eosinophil concentrations. Decreased eosinophil-count stability may be related to a wide range of clinical circumstances such as exacerbations and corticosteroid treatment [4]. However, eosinophil blood count measured over a mean period of 28 days seems to be stable, indicating that a single count is feasible to identify COPD phenotype [5].

Bacteria's play a major role in exacerbations of COPD. There is an inverse correlation between sputum eosinophilia and airway bacterial load during the stable state, while bacterial exacerbations in COPD are associated with a decrease in blood eosinophils [6]. Physiopathological pathways linked to reduced eosinophil counts during bacterial infection are not yet fully understood, although adrenal glucocorticoid stimulation, promptly migration of eosinophils to inflammatory site and innate immune response appear to be key factors. Relationship between eosinophil measurements and bacterial counts may be critical determinants to predict corticosteroid treatment response.

For the present, it remains unclear if blood eosinophilia may predict worse prognosis of COPD. In representative US population-based cohort [7], increased blood eosinophil levels (Eos) levels were associated with older age, male gender, and severe asthma. A greater progression of emphysema and worsening in SGRQ score was observed in patients with persistent lower Eos counts. COPD patients with lower Eos (< 2%) also exhibited an increased risk of co-morbidities (i.e., anemia and CHF) and may be less responsive to corticosteroids, requiring closer clinical monitoring. Górska., *et al.* [8] recently reported that neutrophilic phenotype of COPD was associated with more severe airway obstruction and hyperinflation. Results from another cross-sectional study support an inverse relationship between the sputum eosinophilia and FEV_1. Patients with bronchodilator reversibility had higher eosinophil counts, although FEV_1 reversibility was not associated with atopy or asthma [1].

There has been a lot of debate about optimal thresholds of blood eosinophils to define eosinophilic phenotype and guiding Inhaled corticosteroid (ICS) treatment in stable COPD. In a substantial proportion of patients, elevated eosinophil concentrations have been correlated to ICS response. A recent meta-analysis [2] compared patients with eosinophil counts of < 2% and > 2% in terms of the risk of

exacerbation, time-of-first exacerbation, and pneumonia events. Overall, ICS subgroup with Eos > 2% had a significantly reduced RR of moderate/severe exacerbations. In a post hoc analysis of the Withdrawal of Inhaled Steroids during Optimized Bronchodilator Management (WISDOM) study, ICS withdrawal leaded to a pattern of increasing moderate/severe exacerbation frequency in Eos thresholds of ≥ 4% or ≥ 300 cells/μL [4]. FLAME (Effect of Indacaterol Glycopyronium vs Fluticasone Salmeterol on COPD Exacerbations) study [9] found no association between baseline eosinophils and response to ICS treatment. LABA/LAMA subgroup experienced fewer hospitalizations and was significantly superior to LABA/ICS for prevention of exacerbations in the < 2%, ≥ 2%, < 3%, < 5% Eos subgroups. In a real world large observational study [10], initial treatment with LABA/ICS was more effective at reducing COPD exacerbation than LAMAs, mainly tiotropium, among patients with blood eosinophil concentration greater than 4% or ≥ 300 cells/μL. Both treatments were equally effective at preventing exacerbation among patients with a Eos < 4% of the total white blood count. Another critical concern is a significant two-fold increased risk of pneumonia events in patients under ICS-containing treatment.

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), hospitalization due to acute exacerbation is correlated with massive impact in quality of life and poor long-term prognosis. In a retrospective study [11], increased blood eosinophils at hospital admission in patients with severe exacerbation was associated with an increased risk of 12-month COPD-related and all-cause readmission, besides a shorter time to first COPD-related readmission. These findings emphasize the potential role of blood eosinophil cell counts in COPD as a biomarker to predict hospital readmissions throughout the course of the disease in corticosteroid-naive patients.

It is widely agreed that preventing exacerbation remains a key feature in effective COPD care. Identifying properly an eosinophilic phenotype allow precise and effective treatment strategies in order to improve quality of life and minimize adverse outcomes. Blood eosinophil count is a simple tool which might guide bedside decision and influence our future perspectives on the optimal management of patients with COPD.

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