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Clinical Research Progress of Peripheral Blood Eosinophils in Chronic Obstructive Pulmonary Disease

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Abstract: Chronic obstructive pulmonary disease (COPD) accounts for one of the major health and economic burdens worldwide. As a heterogeneous disease, the underlying inflammatory pattern of COPD differs from the previously thought neutrophil-dominated inflammation, with eosinophilic inflammation occupying approximately one third of stable COPD. Although the eosinophil (EOS) threshold associated with clinical relevance in patients with COPD is currently debated, eosinophil count can be used as a biomarker to guide treatment and to assess the risk of acute exacerbations of COPD, the efficacy of inhaled corticosteroids, and clinical outcomes. The purpose of this review is to describe the biological characteristics of eosinophils and the related research progress as clinical biomarkers.

Keywords: Chronic obstructive pulmonary disease; Eosinophils; Biomarkers

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1. Introduction

Chronic obstructive pulmonary disease (COPD) is a common chronic disease of the respiratory system characterized by persistent respiratory symptoms and airflow limitation [1]. COPD is one of the leading causes of mortality events worldwide, and as the severity of COPD symptoms and exacerbations increases, patients' quality of life declines and healthcare costs rise, significantly increasing the global healthcare economic burden [2,3]. In this paper, we review the biological characteristics, threshold and stability of eosinophils, their relationship with COPD exacerbations, disease progression, and treatment outcomes. It aims to provide reference information for clinical research and comprehensive therapeutic interventions for related diseases.

2. Biological characteristics of eosinophils

Eosinophils (EOS) are important immune effector and inflammatory cells. They have multiple functions and play a role in homeostasis and disease in various tissues, including the lungs [4,5]. Normally, EOS remain quiescent in the peripheral blood, whereas when exposed to pro-inflammatory factors such as IL-3 and IL-5, EOS are

partially activated and may migrate to sites of inflammation [6,7]. EOS are derived from hematopoietic stem cells in the bone marrow, which are released into the bloodstream upon maturation, and then travel to various sites such as the thymus and the intestine [8,9]. Normally EOS are not present in lung tissues, and their accumulation in the lungs is considered to be an abnormal inflammatory response in the lungs [10,11].

3. Threshold and stability of eosinophils

The level of eosinophils in the lungs can be detected by means of induced sputum, alveolar lavage fluid, and percutaneous lung puncture tissue [10]. It is important to note that these EOS counts reflect overall levels and do not express activated EOS. studies have shown that blood EOS concentrations are generally considered to be a good predictor of EOS concentrations in the airways. There is a lack of consensus on the appropriate threshold used to define eosinophilic inflammation in COPD. The use of a single threshold to guide all treatments is not justified because of the different amounts of EOS during stable disease, acute exacerbations, and after treatment [11-13], and because EOS in peripheral blood fluctuates widely within the same individual. Previous studies have shown that thresholds for sputum EOS have been set at 1% [14], 2% [15], and 3% [16] to define COPD eosinophilic inflammation, respectively, whereas the threshold for blood EOS is mostly set at 2% [17]. However, some of these thresholds are set with reference to the setting of EOS counts in asthma and therefore may not correspond to the optimal threshold for COPD. In the WISDOM study, researchers analyzed the rate of COPD exacerbation by discontinuation of inhaled corticosteroids (ICS) by setting the blood EOS thresholds at 150–400 counts/μL and 2–6%, respectively. The results showed that the thresholds for the most significant deleterious effects of ICS discontinuation on exacerbation risk were observed to be ≥ 4% or ≥ 300 cells/μL. The cutoff value for EOS is not clearly defined, and most of the existing studies have adopted the use of more than 2% (~150 cells/μL) as the cutoff value for experimental studies [18-21].

4. Blood eosinophils and risk of acute exacerbation of COPD

Several studies in recent years have supported a correlation between high EOS and acute exacerbations of COPD [22-26]. Vedel-Krogh *et al.* noted that EOS counts were increased in acute exacerbations of COPD compared to stable phases [27-29], whereas other studies have reported an association between increased EOS counts and increased risk of exacerbations. In a 1-year observational study with 182 acute exacerbation events in 86 COPD patients, the researchers identified four acute exacerbation phenotypes: bacterial, viral, eosinophilic, and oligoinflammatory, with an increased EOS accounting for 28% of the total [30], suggesting that EOS occupies an important role in acute exacerbations of COPD [31].

5. Response of blood eosinophils to ICS treatment in COPD

Regular use of ICS, either alone or in combination with long-acting β2 agonists (LABA), reduces the risk of developing COPD exacerbations [30]. Several studies have found that elevated eosinophil concentrations predict response to ICS in COPD patients [32,33]. Pavord *et al.* [23] conducted a post-hoc analysis of three studies of ≥ 1 year duration and found that the use of ICS/LABA was significantly associated with the rate of acute exacerbations of COPD compared to the long-acting muscarinic inhibitor (LAMA) or placebo groups, whereas the proportion of EOS below 2% was not significantly different between groups. In addition, a post hoc analysis by Watz *et al.* [34] in the WISDOM trial showed that blood EOS counts were associated with exacerbation rates after complete discontinuation of medication in patients with severe and very severe COPD, and that patients with high blood

EOS counts tended to be more sensitive to discontinuation of ICS from the ICS-LABA-LAMA combination. The difference in exacerbation rates between patients who continued ICS therapy and those who discontinued ICS therapy increased with increasing blood eosinophil thresholds [19]. Another pooled study [35] used blood EOS ≥ 100 per μL as a threshold and found that 79% of subjects were able to reduce the frequency of acute exacerbations with ICS/LABA compared to LAMA alone. In the same study, only eosinophil count and smoking status were found to be independent predictors of response to ICS in a population of COPD patients, with the benefit of ICS treatment most pronounced in smokers with high blood EOS counts. In contrast, in a 52-week randomized controlled trial with a large sample conducted by Wedzicha *et al.* [36] found a lower risk of acute exacerbation in the LAMA/LABA group compared to the ICS/LABA group, and in a stratified analysis using a blood EOS of 2% as a threshold, the efficacy of the LAMA/LABA group was superior to that of the ICS/LABA group, regardless of whether the blood EOS was ≥ 2% or < 2%. In contrast, Barnes *et al.* performed a post hoc analysis of the ISOLDE results [37], which showed that the acute exacerbation rate in the ICS/LABA group was not significantly different from that in the placebo group regardless of whether blood EOS was > 2%, meaning that the effect of blood EOS on the benefit of ICS was not significant. In addition, when analyzing the FLAME study [38], LABA/LAMA efficacy was not inferior to ICS/LABA in all subgroups with blood EOS thresholds set at 2%, 3%, 5%, 150/μL, and 300/μL, respectively.

6. The relationship between blood eosinophils and prognosis of COPD patients

Acute exacerbation of COPD is closely related to the prognosis of patients, causing a decline in lung function and quality of life, which in turn increases the risk of death [39]. The above studies have shown that elevated blood eosinophil counts are associated with an increased risk of acute exacerbation. Several studies in recent years have proposed that blood eosinophils can be used as an alternative biomarker of eosinophilic airway inflammation and as an indicator of response to ICS in patients with stable chronic COPD [40].

Hospers *et al.* [41] found that peripheral blood EOS counts were associated with 30-year all-cause mortality in a long-term SPIROMICS cohort study. Saltürk *et al.* [42] conducted a retrospective observational cohort study of patients with acute exacerbations of COPD in the intensive care unit (ICU) and found that patients in the COPD exacerbation group with a blood EOS of ≤ 2% (non-eosinophilic group) had higher APACHE II scores on admission, poorer arterial blood gas scores, the use of noninvasive mechanical ventilation (NIMV) at the beginning of treatment, and had higher failure rates, longer hospital stays, significantly higher rates of septic shock and infection with drug-resistant pathogens, and an increased ICU mortality rate [42]. Bafadhel *et al.* [43] enrolled 243 patients with acute exacerbations of COPD from two centers in a prospective study, defining blood EOS counts ≥ 200/μL or ≥ 2% as EOS-elevated, and showed that patients with elevated EOS usually had shorter hospital stays, but there was no significant difference in long-term mortality or rehospitalization rates.

7. Conclusion

COPD is a heterogeneous disease and the biological mechanisms involved in its development and progression are not yet fully revealed. Eosinophils can be used as a blood indicator of eosinophilic airway inflammation in patients with clinical COPD and can be used to guide therapeutic choices for ICS in patients with COPD to maximize the benefit of clinical care for patients. Eosinophils are mediators of inflammation in many COPD patients. Although the threshold for defining eosinophilic inflammation in the context of COPD has not been established, elevated blood EOS counts have been associated with reduced lung function and increased risk of exacerbations in patients with COPD. In addition, a reduction in eosinophilic inflammation is associated with a

decrease in the frequency of exacerbations. COPD patients with evidence of eosinophilic inflammation usually respond better to ICS therapy.

Disclosure statement

The author declares no conflict of interest.

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