Review on the correlation between chronic obstructive pulmonary disease and eosinophil in peripheral blood

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Abstract
Chronic obstructive pulmonary disease (COPD) is an irreversible disease characterized by the limitation of continuous airflow. Eosinophil (EOS) in peripheral blood plays a key role in the acute exacerbation of COPD. Eosinophil-increased COPD has become an important variant of COPD and the focus of individualized treatment of COPD. Numerous studies have shown that an increased eosinophil count or an increased percentage in the peripheral blood closely correlates to the acute exacerbation and prognosis of COPD. Therefore, this study intends to review the progress of domestic and foreign research on the correlation between COPD and EOS.

Keywords
airway inflammation, biomarker, chronic obstructive pulmonary disease, eosinophil in peripheral blood, inhaled glucocorticoids

Introduction
Chronic obstructive pulmonary disease (COPD) is an irreversible disease characterized by the restriction of continuous airflow. At present, epidemiological data show that the prevalence of COPD is 8.6% in adults over 20 years, 13.7% in adults over 40 years, and over 27% in adults over 60 years.¹ The Global Burden of Disease Research project points out that COPD will rank fifth in the world for economic burdens in 2020 and will become the third leading cause of death in the world.² Worsening of the illness is associated with poor quality of life and increased incidence rate and mortality.³ The GOLD report in 2017 clarified the value of the eosinophil (EOS) count in the risk judgment of acute exacerbation, and peripheral blood EOS count can be used as a biomarker to predict the risk of acute exacerbation of COPD in patients.⁴

Correlation between EOS and airway inflammation
In 1879, Paul Ehrlich first described EOS. EOS usually accounts for less than 5% of peripheral blood leukocytes, and its lifespan in the circulation of the peripheral blood is less than 18 h. EOS has four basic proteins that are harmful to bronchial epithelial cells, including eosinophil cationic protein (ECP), major basic protein (MBP), eosinophil peroxidase (EPO),
and eosinophil-derived neurotoxin (EDN). In patients with COPD, the level of EOS increases, and the levels of ECP, MBP, and EPO are elevated, suggesting that EOS may be activated and degranulated in the course of COPD, which correlates to airway inflammation damage.\(^5\) COPD has different phenotypes at the cellular level; in addition to the inflammation caused by neutrophils, it is also closely correlated to EOS.\(^5\) Hikichi et al.\(^7\) reported that there was a certain correlation between the increase of sputum EOS and the bronchial hyperresponsiveness in patients with COPD. Previous studies have confirmed that EOS can be used as a marker of airway inflammation, and more than 20% of COPD in patients is caused by eosinophilic inflammation.\(^6\) Peripheral blood ECP has a cytotoxic effect, which not only embodies the activation function of EOS but can also induce mast cells to produce histamine and destroy the normal airway tissue function. It has a strong cytotoxic and neurotoxic effect and has a synergistic effect with the body’s inflammatory transmitter, causing damage to the function of bronchial epithelium and stromal cells, tissue damage, congestion, and edema of the bronchial mucosa. It can trigger the body’s inflammatory response, thus aggravating the condition and promoting the occurrence of allergic inflammation.\(^5,9\)

**The correlation between eosinophilia and acute exacerbation of COPD**

In 2017, the GOLD report emphasized that EOS could be used as one of the biomarkers for the acute exacerbation of COPD. Eosinophilic inflammation can be observed in peripheral blood and sputum samples of patients with COPD.\(^10,11\) During the deterioration period, airway inflammation increases, and inflammation in patients with COPD is mainly neutrophilic. In some patients, it is related to an increase in the EOS count in sputum by more than 3%\(^12,13\). A study has revealed that the increase of eosinophil in the peripheral blood of patients with COPD in the stable phase will increase the frequency of acute exacerbation.\(^14\) Clinical research shows that patients with an acute exacerbation of COPD often have eosinophilic cell elevation.\(^15\) Therefore, the detection of EOS in patients with COPD has an important clinical reference value.\(^16–18\)

A study has revealed a correlation between eosinophilia and chronic bronchitis and COPD deterioration.\(^18\) The level of EOS in peripheral blood has a high reference value for the diagnosis of COPD. For patients with COPD, eosinophil in the peripheral blood above \(0.34 \times 10^9/L\) will increase the risk of serious deterioration by 1.76 times.\(^19\)

**Selection of a sample and boundary value of EOS test**

The increase of EOS in sputum samples is a direct manifestation of EOS airway inflammation. There is also an increase in EOS in sputum samples in some patients with COPD who do not receive inhaled corticosteroid (ICS) treatment. Therefore, the increase in EOS in sputum samples means EOS airway inflammation correlates with sensitivity to glucocorticoid treatment. However, induced sputum detection is too complex, has weak clinical practicability, and is difficult to popularize. Experts domestically and abroad have started to explore more convenient and effective biomarkers. EOS in peripheral blood has gradually attracted attention. Results of peripheral blood EOS are more easily obtained and can predict EOS airway inflammation. Related studies suggested that for patients with stable and acute exacerbation phases of COPD, when the critical value of the percentage of EOS in peripheral blood was set as 2%, the sensitivity of clinically related indexes was good,\(^20,21\) with 2% as the critical value having good specificity.\(^22\) A higher than 2% peripheral blood EOS count is associated with an increased risk of moderate to severe exacerbation.\(^23\) The mortality of patients with COPD and high EOS count and asthma in the late-stage increases. Rogliani et al.\(^24\) retrospectively analyzed the trend of pulmonary function examination in patients with COPD over time, based on two baseline EOS count layers (<2% (EOS−) and \(\geq 2\% \) (EOS+))). The results revealed a difference in the decrease of forced expiratory volume in 1 s (FEV1) and FVC between subjects in the EOS− group and EOS+ group. The comprehensive evaluation results revealed that different levels of peripheral blood EOS in the two groups might independently affect the time course of the pulmonary function test. Two subgroups with specific disease characteristics were identified, respectively: excessive hyperemia and rapid decline.\(^24\) In the ECLIPSE cohort study, complete data from 1483 patients with COPD were included in the analysis, and peripheral blood EOS levels were measured at baseline, 1–3 years subsequently. In
every follow-up, the cases with continuous peripheral blood EOS $\geq 2\%$ accounted for 37.4%, the cases with intermittent peripheral blood EOS (at least once peripheral blood EOS) $\geq 2\%$ accounted for 49%, and the cases with EOS $\geq 2\%$ only accounted for 13.6%. In addition, a previous study reported that there was a more rapid decline in people with healthy FEV1 and patients with airway disease with higher peripheral blood eosinophil counts, and ICS could be used as a primary preventative treatment to modify this.  

Pavord et al. analyzed ten new COPD drugs, with the results revealing that 63% of 10,861 patients had baseline peripheral blood EOS $\geq 2\%$, with 2% as the cut-off value. In addition, 2% was selected as the cut-off value in large-scale research studies such as INSERT, FORWARD, and WISDOM. The distribution of EOS in patients with COPD in the United Kingdom and the United States is similar to that in other countries. EOS absolute count results revealed that FEV1 decreased, and the risk of acute exacerbation increased in patients with COPD who had increased EOS in peripheral blood ($\geq 300/\mu l$) after the withdrawal of ICS. At present, the optimal value and unit (absolute value or percentage) of high or low EOS in peripheral blood in patients with COPD is not unified. The most common cut-off value is 2% of EOS in total leukocyte count in peripheral blood, or 150–400 cells/μl of absolute EOS in peripheral blood. After integrating the results of post-event analysis, pre-set analysis, and ICS withdrawal in multiple studies, GOLD2019 determined that ICS might have the most benefit when the peripheral blood EOS count was 300 cells/μl.

The correlation between the increase of EOS and the application of glucocorticoids

Glucocorticoid (including inhaled glucocorticoid) is an important treatment for COPD. Although there can be many adverse reactions in the use of glucocorticoids, these remain the first choice of treatment for patients with acute exacerbation of COPD. COPD has many phenotypes, and the response of glucocorticoids to EOS is good. A previous study revealed that systemic use of glucocorticoids in patients with COPD exacerbation could quickly restore lung function (the improvement rate of FEV1 on the first day was 0.11 higher than that of the placebo group) and found that the course of the disease was shortened and the cure rate increased. There is a direct correlation between the increase of peripheral blood EOS and the positive response of glucocorticoid therapy in patients with COPD. Pavord et al. revealed that data regarding EOS count was significant for 10,861 patients with COPD, with a 2% EOS count as the cut-off value. The incidence of pneumonia was higher in patients with COPD and a lower peripheral blood EOS count than in patients with COPD and a higher peripheral blood EOS count. Patients with an EOS count of less than 2% had a poor response to ICS. The results of previous studies have revealed that short-term oral administration of prednisolone could significantly improve FEV1 in patients with COPD, and patients with an EOS level $\geq 2\%$ benefited more than patients with an EOS level $<2\%$. Hilton et al. concluded, through data analysis, that the EOS count was used as a biomarker of the response to ICS in patients with COPD. In their study, Bafadhel et al. revealed that prednisolone was more effective in patients with acute exacerbation of COPD and an increased EOS level. The peripheral blood EOS was high in the acute exacerbation stage of COPD, and applying glucocorticoid could effectively relieve symptoms, which was of great significance for the diagnosis and treatment of COPD and the evaluation of the effect of anti-inflammatory treatment.

Correlation between EOS count and prognosis of COPD

EOS count affects the prognosis of COPD. There is a significant correlation between the proportion of EOS in peripheral blood and the therapeutic effect and clinical prognosis of COPD. Patients with COPD and a peripheral blood EOS of $>2\%$ had a better prognosis. Pascoe et al. carried out a comparative analysis of 3177 patients with moderate to severe COPD. The results revealed that for patients with COPD who did not receive ICS treatment, the higher the peripheral blood EOS value and acute aggravation rate was. For those who received ICS treatment, there was no correlation between peripheral blood EOS and acute exacerbation rate. However, increased eosinophils in COPD are not considered a characteristic feature of the disease and that eosinophils are elevated in some COPD patients.
The newly released GOLD report (2020) explicitly uses peripheral blood EOS as a biomarker to guide ICS and ICS descending treatment for the first time. However, a previous study revealed that there was still a big fluctuation in EOS, and different race and disease characteristics may also affect the selection of a critical value. Therefore, in the future, more prospective studies are needed to confirm the clinical value of EOS in COPD.

Conclusion
In recent years, COPD with peripheral eosinophilia has become an important research direction for the individualized treatment of the disease. Previous studies have confirmed a significant correlation between peripheral blood EOS and acute exacerbation of COPD, and several studies have confirmed the correlation between the increase of peripheral blood EOS and the difference in therapeutic effect between ICS/LABA and LABA. However, the critical values of peripheral blood EOS in different studies is not unified. This may be related to the differences in patient baseline characteristics and study methods.

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