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Blood eosinophil level to predict chronic obstructive pulmonary disease clinical outcomes: not ready yet

Cheng-Sen Cai, Jun Wang

Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong 250001, China.

Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease. By 2020, COPD will become the third leading cause of death. Eosinophil is a component of T-helper 2 cell-mediated immunity and has an arsenal of antimicrobial defenses. A large quantity of eosinophils are released into the blood circulation from bone marrow after inflammation and they will be recruited to the airway and other tissues through chemokine-mediated chemotaxis to initiate and upregulate the immune response [Figure 1].[1]

Recent studies have found that the level of blood eosinophil correlates with the risk of acute exacerbation,[2] the incidence of pneumonia,[3] and the responsiveness to inhaled corticosteroids (ICSs).[4] It is worth noting that as the disease progresses, patients with relatively stable eosinophil level (blood eosinophil counts persistently lower than 2%) will experience emphysema progression and a slight improvement in St. George's Respiratory Questionnaire scores (1.6 units).[5] Some scholars have proposed that blood eosinophils can be used as a new marker for disease progression and treatment in patients with COPD. However, the results of relevant studies are quite different or even contrary. It is uncertain that blood eosinophils can be used as a reliable marker for COPD. This paper enumerated several aspects of relevant research with varying conclusions and explored the underlying factors.

Researchers could not reach a consensus understanding regarding the correlation of eosinophil levels between blood and lung tissue. In theory, eosinophils will spread to the bronchial mucosa and lung tissue after airway inflammation. Therefore, eosinophil levels in blood should correlate with those in the sputum, lavage fluid, and tracheal mucosa. The correlation between sputum and blood has been bolstered in previous studies.[6,7] Eltboli et al[8] found that blood eosinophil levels were positively correlated with lung tissue eosinophil levels ($r = 0.57$, $P = 0.009$). Concurrently, Hartjes et al[9] conducted a more comprehensive study on 114 patients with COPD. The levels of eosinophil in the blood, sputum, lavage fluid, and lung tissue were measured. They found that the level of eosinophil in blood was positively correlated with that in the other three specimens. However, Turato et al[10] found no correlation between the blood and airway as well as the lung tissues ($r = 0.22$, $P = 0.42$; $r = 0.20$, $P = 0.31$; lung $r = 0.26$, $P = 0.12$, respectively) in 36 patients with COPD who were undergoing local pneumonectomy for pulmonary nodules.

Can patients with COPD with high eosinophil levels benefit from ICS? Several clinical observations have shown that the risk of acute exacerbations increases with the elevation of blood eosinophil levels.[2,4] However, the correlation between them remains controversial.

Pascoe et al[4] carried out post hoc analyses on two large clinical studies related to patients with COPD. They found that the ICS + long-acting β2-agonist (LABA) group could significantly reduce the frequency of acute exacerbation by 19% compared with that in the LABA group in patients whose blood eosinophil level was higher than 2%. However, Barnes et al[11] reanalyzed the Inhaled Steroids in Obstructive Lung Disease in Europe study and found that the average rate of acute exacerbations decreased more significantly in patients whose blood eosinophil level was less than 2% than in patients whose blood eosinophil level was greater than 2% (1.32 times per year *vs.* 1.63 times per year, $P = 0.009$). This contradictory result suggested that patients could benefit from lower blood eosinophil levels. In addition, Wedzicha et al[12] conducted similar analyses in the Effect of Indacaterol Glycopyronium vs Fluticasone Salmeterol on COPD Exacerbations

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Correspondence to: Dr. Jun Wang, Department of Respiratory and Critical Care Medicine, Second Affiliated Hospital of Shandong University of Traditional Chinese Medicine, Jinan, Shandong 250001, China
E-Mail: jnwj660606@163.com

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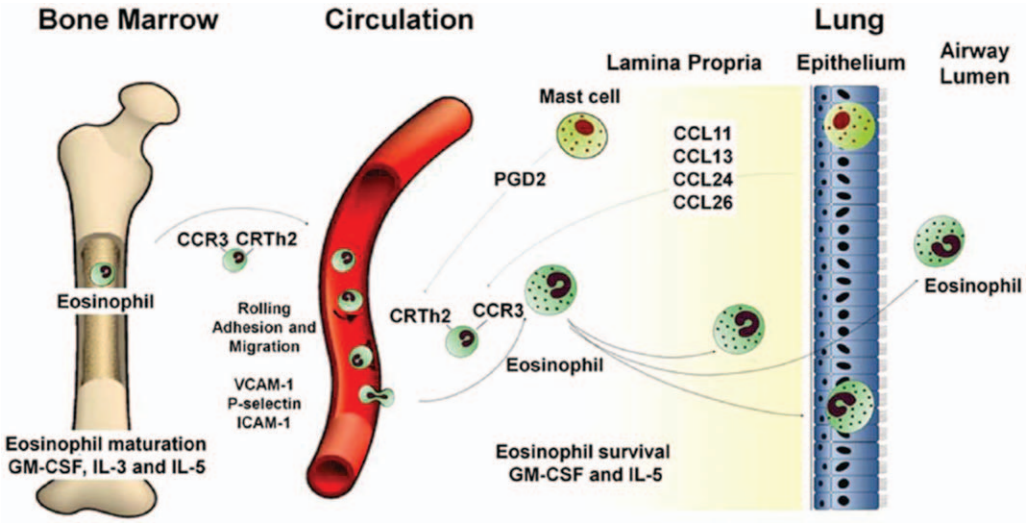

Figure 1: Eosinophil trafficking from the bone marrow to the airway. (Notes: referred from George L, Brightling CE[1] with their permission).

(FLAME) study. After 12 months of treatment (ICS + LABA group and LABA + long-acting muscarinic antagonist [LAMA] group), the rate was significantly lower in the LABA + LAMA group than in the ICS + LABA group, irrespective of the level of blood eosinophil.

Correlation between reduced eosinophil levels and the incidence of pneumonia remains uncertain. It was found that the incidence of pneumonia changed significantly with the level of blood eosinophil while using ICS. However, there is no clearly defined mechanism of low eosinophils affecting pneumonia in COPD.

Pavord et al[3] conducted a meta-analysis including ten large clinical trials with 10,861 patients with COPD. They found that the lower the blood eosinophil level (<2%) was the more pneumonia occurred in patients (3.7% *vs.* 3.2%). They speculated that higher eosinophil levels might reflect an improved capacity to clear lung infections before progression to pneumonia. Conversely, a lower eosinophil level might indicate increased susceptibility to pneumonia or be acquired as a consequence of a recent infection. Similarly, Pascoe et al[4] found the same results in patients using veratrol (LABA) alone. The authors also analyzed patients with COPD using LABA and full-dose ICS and found that the eosinophil level was not related to the incidence of pneumonia.[3] Similarly, Vedel-Krogh et al[13] found the same results in patients with COPD with forced expiratory volume in 1 s <50% ($P = 0.78$). This finding indicated that the incidence of pneumonia was not related to the level of blood eosinophil.

Considering the reason for the different results of relevant studies, there are several factors to consider as explanations. (1) The conditions of the COPD subjects are different. Many clinical studies selected patients with moderate and severe COPD.[2,4] Few studies have focused on patients with severe or extremely severe COPD.[14] However, some studied included patients who met the diagnosis standard and ignored the severity of COPD,[7] whereas some studies were based on the different severity of COPD exacerbation.[15] Notably, the term "the severity of COPD patients" is not equal to "the severity of acute exacerbation of COPD patients." (2) In the study of the relationship between ICS and blood eosinophils, there were various treatment methods, such as ICS *vs.* placebo[16]; ICS + LABA *vs.* LABA[3]; and ICS + LABA *vs.* LABA + LAMA.[12] The level of blood eosinophil might be influenced when using LABA and LAMA jointly or each separately. Furthermore, different doses of these compounds (ICS, LABA, and LAMA) might result in statistically different blood eosinophil levels. (3) The differences between inclusion and exclusion criteria matter to the research results. Elevated eosinophil levels can be seen in patients with asthma-COPD overlap and patients with a history of asthma. Therefore, the level of blood eosinophil might be affected in the research if they were not excluded.[8,17] In addition, different studies were of varying lengths of elution period. They were ranged from 8 weeks[11] to 6 months[9] or even had no elution period.[2] (4) The cutoff values are varied and have not come to an agreement yet. Several studies set the cutoff value at 2% (blood eosinophil percentage) in predicting COPD exacerbation and ICS benefit because it has a sensitivity of 90% and specificity of 60% for identifying a sputum eosinophilia.[7] However, while Singh et al[5]found blood eosinophil percentage was unstable and 2% (blood eosinophil percentage) was not a convincing threshold, Vedel-Krogh et al[2] found that the total number of blood eosinophil count was more accurate and set the blood eosinophil count at 340 cells/μL in predicting severe exacerbations. Meanwhile, the Global Initiative for Chronic Obstructive Lung Disease guideline cite the study reported by Bafadhel et al[18] that patients with blood eosinophil level lower than 100 cells/μL had little or no effect on ICS. Besides, the guideline recommends that patients with COPD with blood eosinophil level higher than 300 cells/μL would benefit more from ICS. (5) The stability of blood eosinophil level remains controversial. Currently, there is a lack of research on the stability of the

blood eosinophil level. Barnes et al[11] found that the average percentage of blood eosinophil had little variation (cutoff value: 2%) in patients with COPD. However, Singh et al[5] made a tracking comparison of each patient's blood eosinophil level. By using 2% of blood eosinophil percentage as cutoff value, the author found that 728 (49%) subjects had variable eosinophil counts, oscillating above and below 2% over 3 years of observation. (6) Many post hoc analyses were conducted based on current clinical studies.[3,4,8,11,14] More basic researches on the molecular mechanism are warranted.

In conclusion, eosinophil as a blood marker of COPD remains controversial. Furthermore, more basic and systematic experiments are needed to clarify the pathogenesis of blood eosinophils in patients with COPD to better serve the clinic in the future.

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Conflict of interest

None.

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