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【 REVIEW ARTICLE 】

Measurement of Blood Eosinophils in Asthma and Chronic Obstructive Pulmonary Disease

Tsunahiko Hirano and Kazuto Matsunaga

Abstract:
Eosinophils are important effector cells in airway inflammation, as pleiotropy and heterogeneity can be linked to various pathophysiologies in asthma and chronic obstructive pulmonary disease (COPD). Sputum eosinophils can reflect the heterogeneity of airway inflammation, and owing to their traits, blood eosinophils can be a surrogate and potential biomarker for managing both conditions. Blood eosinophils are activated via the stimulation of type 2 cytokines, such as interleukin (IL)-5, IL-4/13, granulocyte-macrophage colony-stimulating factor, IL-33, and thymic stromal lymphopoietin. There is sufficient evidence to support the relationship between the blood eosinophil count and clinical outcomes, including pulmonary function decline, exacerbations, all-cause mortality, and treatment response to inhaled corticosteroids and biologics. Thus, there is growing interest in the use of blood eosinophils for the management of these diseases. Compiling recent evidence, we herein review the significance of measuring blood eosinophils in asthma and COPD.

Key words: eosinophil, asthma, COPD, blood, biomarker, biologics

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1. Importance of Evaluating Blood Eosinophilia in Asthma and COPD

Asthma and chronic obstructive pulmonary disease (COPD) are chronic inflammatory diseases of the airways with various patterns of inflammation. Both conditions are mediated by up- or downregulation of numerous inflammatory cells and signals. However, while the two conditions have similar clinical manifestations, there are distinct gaps in the inflammatory patterns of the airways with respect to the involvement of different inflammatory cells, signals, and responses to treatment.

The representative inflammatory cells of the airway in asthma are eosinophils, while those in COPD are neutrophils. However, there are also phenotypes of COPD in which eosinophilic inflammation of the airway is predominant under certain circumstances, such as exacerbation or asthma overlap. This means that eosinophilic inflammation of the airway in both diseases is a promising therapeutic target, as sputum eosinophilia can predict clinical outcomes, such as symptoms, pulmonary function decline, exacerbation, mortality, corticosteroid use (1) as well as the response of type 2 biologic agents (2). However, it is difficult for clinicians to measure the inflammatory status of the airways with a sputum examination due to the complicated processing. Instead, in the real-world clinical setting, blood eosinophil counts are measured as a surrogate marker of eosinophilic airway inflammation and have been shown to be significantly correlated with airway eosinophils (3-6).

Although interleukin (IL)-5 plays a crucial role in the eosinophil differentiation, maturation, activation, and survival of bone marrow $CD34^+$ eosinophil progenitor cells, the eosinophil count is low because IL-5 is regulated under normal conditions, such as in healthy individuals (7). However, under chronic airway inflammation conditions, such as asthma and COPD, various cytokines, including IL-5, IL-3, granulocyte-macrophage colony-stimulating factor, IL-33, and thymic stromal lymphopoietin, are upregulated and promote this cascade (8). Consequently, the number of circulating eosinophils is speculated to increase. Therefore, these molecules are responsible for blood eosinophilia and serve as therapeutic targets for the treatment of asthma and COPD.

Department of Respiratory Medicine and Infectious Disease, Graduate School of Medicine, Yamaguchi University, Japan
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Correspondence to Dr. Tsunahiko Hirano, tsuna@yamaguchi-u.ac.jp

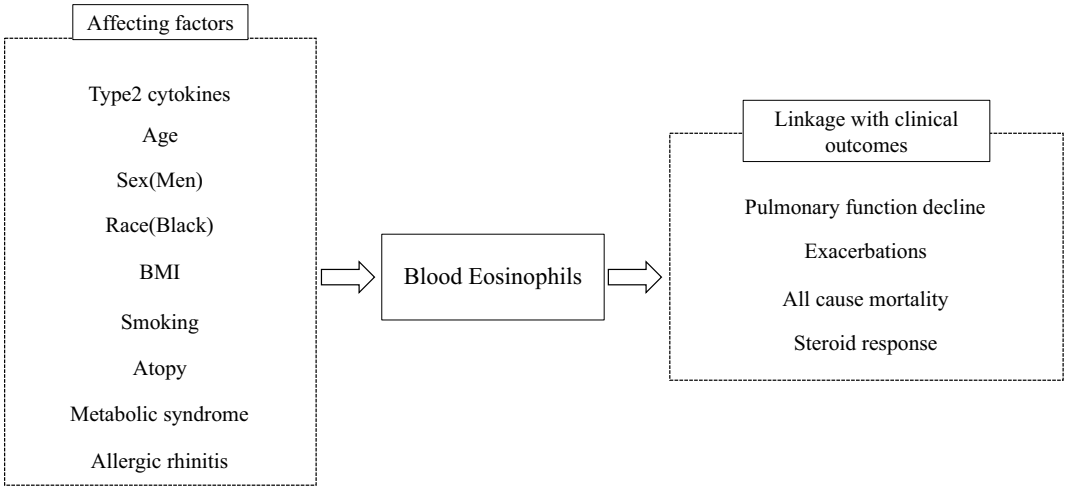

Figure 1. Relationship between influential factors and clinical outcomes via blood eosinophilia.

2. Relationship between Blood Eosinophilia and Clinical Outcomes of Asthma and COPD

Since eosinophils express diverse mediators and secrete specific proteins (9, 10), pleiotropy and heterogeneity may be associated with various clinical outcomes, listed below.

A. Stability and diagnostic accuracy of blood eosinophil for distinguishing eosinophilic and non-eosinophilic airway inflammation

While eosinophils can serve as promising biomarkers for airway diseases, their biological stability remains a critical issue in clinical settings. Several studies have assessed the stability of blood eosinophils (4, 11). It has been shown that when the mean blood eosinophil count in the general population was 128 cells/μL, the cut-off point of the 75th percentile was 210 cells/μL (12). However, as blood eosinophils are influenced by clinical parameters, such as age, smoking, atopy, metabolic syndrome, obesity, and allergic rhinitis (12-14), these effects should be considered when interpreting the pathophysiology or managing asthma and COPD (Fig. 1). In asthma and COPD, sex, race, and the body mass index affect the blood eosinophil count (15). Even if asthma control in patients is stable, the blood eosinophil counts still fluctuate substantially (16). In contrast, while blood eosinophils are stable over time in stable COPD, the counts are unstable in severe acute exacerbation of COPD (AECOPD) because of the variety of causes of AECOPD (17).

A study assessing the diagnostic accuracy of blood eosinophils in airway eosinophilic inflammation of patients with moderate to severe asthma reported that the area under the receiver operating characteristic (ROC) curve (AUC) was 0.89 (95% confidence interval 0.72-0.98) (18). In that report, on setting 270 eosinophils/μL blood as the cut-off, the sensitivity and specificity for diagnosing airway eosinophilic inflammation were estimated to be 60% and 90%, respectively.

B. Pulmonary function decline

There is a correlation between elevated blood eosinophil counts and the forced expiratory volume in 1 second (FEV_1) decline in adults with asthma (19). Similarly, elevated blood eosinophil counts can predict an accelerated pulmonary function decline in COPD (20). This evidence supports the hypothesis that structural lung abnormalities can accompany eosinophilia (20). Furthermore, the blood eosinophil count at an early stage of airway disease may be a predictor of the pulmonary function decline (21).

C. Exacerbation

Blood eosinophilia is correlated with an increased risk of asthma exacerbation (22, 23), so with increasing blood eosinophil counts, exacerbation becomes more severe. However, whether or not the blood eosinophil count can predict exacerbation in COPD remains unclear. The phenotypes of airway inflammation in COPD exacerbation are heterogeneous (24), and eosinophilic predominance in airway inflammation during exacerbation is a clinical phenotype of COPD. However, in moderate COPD exacerbation, blood eosinophil counts ≥2% can be used to detect subpopulations that may benefit from systemic corticosteroid treatment (25). In addition, blood eosinophils of severe COPD exacerbation have been reported to stratify treatment approaches using antibiotics and corticosteroids more effectively than C-reactive protein levels (7).

D. Mortality

High blood eosinophil counts in patients with asthma have been shown to correlate with an increased mortality risk (26). Furthermore, blood eosinophilia in COPD with asthma-like features is associated with an improved survival (27-29). This suggests that the prognosis is better in patients with asthma and COPD with blood eosinophilia receiving appropriate treatment than in those receiving inappropriate treatment and that its estimation is important for

Table. ICS Use Recommendation according to Association between Exacerbation Pattern and Blood Eosinophil.

Eosinophil count	>300 cells/μL	100-300 cells/μL	<100 cells/μL
Exacerbation pattern			
Severe exacerbations or ≥2 moderate exacerbations concomitant asthma	◎	○	△
1 Moderate exacerbation	○	○	△
Repeated infectious pneumonia History of mycobacterial infection	△	△	×

◎, strong ICS use, ○, consider ICS use, △, alternative treatment for ICS, ×, ICS avoid use, moderate exacerbations were defined by the increase of symptoms requiring oral antibiotic and/or a short course of oral steroid therapy, severe exacerbations were defined by the increase of symptoms requiring hospitalization or emergency room visits.

managing these diseases.

E. Treatment response

A blood eosinophil count of >3% or >300 cells/μL can predict clinical outcomes, such as the risk of exacerbation or a good response to corticosteroid treatment, in cases of asthma or COPD (30-35). In asthma, the baseline eosinophil count is a predictor of the response to usual treatments, such as inhaled corticosteroid (ICS) (36-39), and assists in clinical decision-making. Blood eosinophil levels are correlated with airflow limitation, airway hyper-responsiveness, exacerbation, asthma control, and the quality of life (QOL) (40, 41). As the pathophysiology of COPD is heterogeneous, precision medicine is needed to manage this disease. A treatable trait based on phenotypic recognition or on understanding of endotypes is a new identical concept to realize the precision medicine strategy (42). The blood eosinophil count is considered a treatable trait and a relevant biomarker for ICS usage in order to reduce the risk of future exacerbations in COPD (33-35). The Global Initiative for Chronic Obstructive Lung Disease also recommends blood eosinophils be used as a guide for ICS treatment in patients with COPD, based on the exacerbation pattern (43). Cases with blood eosinophils >300 cells/μL with severe exacerbation, ≥2 moderate exacerbations, or a history of concomitant asthma are recommended for strong ICS use. However, when the eosinophil count is <100 cells/μL in groups at high risk for bronchial infection, ICS is not recommended (44). If the blood eosinophil count is 100-300 cells/μL and the patient experiences a moderate exacerbation, ICS use should be considered (Table).

Blood eosinophils play an important role in the pathogenesis of severe asthma. Eosinophilia is associated with the production of several inflammatory cytokines. Since eosinophils specifically express the IL-5 receptor, IL-5 is a key player in eosinophilia, and biologics that can target IL-5 signaling are useful for managing difficult asthma. In fact, a higher baseline blood eosinophil count leads to a greater response of anti-IL-5 monoclonal antibody mepolizumab, resulting in a greater reduction in exacerbations (45). Benralizumab, an IL-5-receptor monoclonal antibody, has also been reported to improve clinical outcomes, such as systemic glucocorticoid overuse, symptoms, the QOL, and exacerbations in the real world (46). A blood eosinophil count ≥150 cells/μL can predict treatment efficacy when biologics are used (45, 47, 48). These findings suggest that eosinophilia can serve as a biomarker for response to biologics.

3. Topics in Blood Eosinophils

A. Phenotype of eosinophils

Inflammatory eosinophils (iEOS) are distinct from the regulatory eosinophil subset, resident eosinophils (rEOS). Although iEOS enhance inflammation, rEOS may have key homeostatic functions. Therefore, the above discrepancies may also be due to differences in the ratio of eosinophil phenotypes between the stable and acute phases (49). However, data on eosinophil phenotypes have mainly originated from mouse studies, and the concept has not been confirmed in humans.

B. ETosis in airway eosinophils

Active cytolytic eosinophil degranulation and cytolytic cell death in the airway have attracted increasing attention. This phenomenon releases eosinophil extracellular chromatin to form DNA via a cytolytic extracellular trap cell death (ETosis) (50). Airway eosinophil ETosis (EETosis) is closely associated with Charcot-Leyden crystal (CLC) formation (51) which contains galectin-10 as a protein component. Extracellular crystallization of galectin-10 is speculated to occur, leading to exacerbation of airway mucus secretion (52).

Conclusion

Eosinophils exhibit pleiotropy and heterogeneity and can be associated with various clinical outcomes, such as a pulmonary function decline, exacerbation, all-cause mortality, and treatment response, in asthma and COPD. In summary, blood eosinophils can serve as surrogate markers for eosinophilic airway inflammation and easily accessible inflamma-

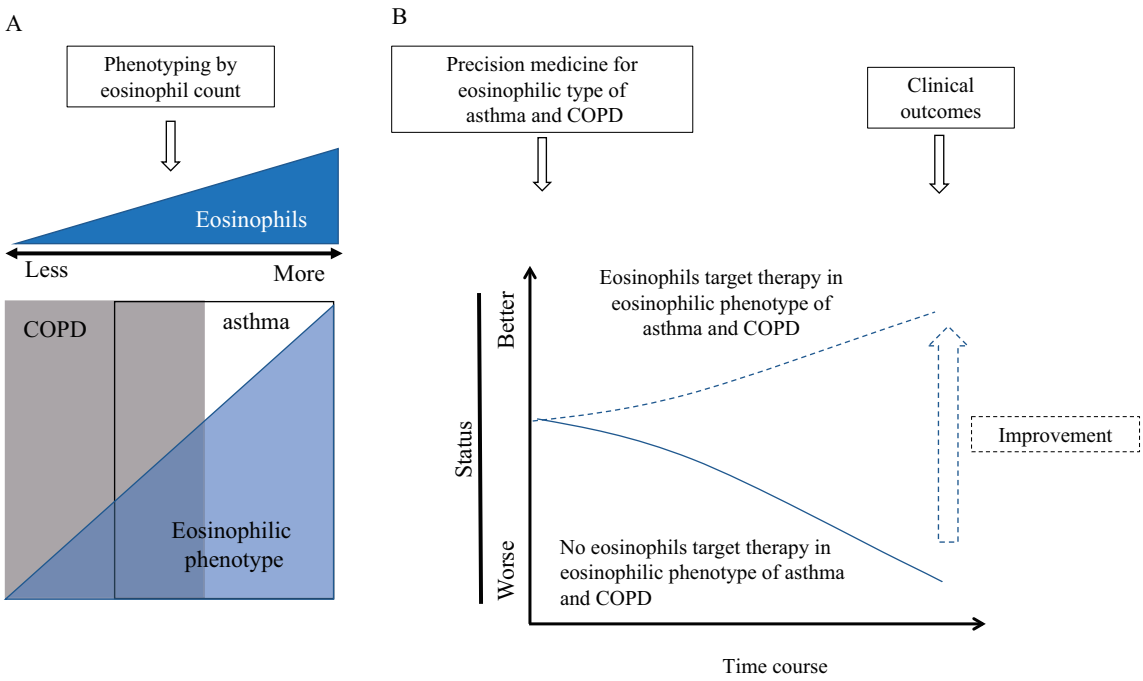

Figure 2. (A) The phenotypic diagnosis based on blood eosinophils. (B) Predicting the effect of targeted treatment by the blood eosinophil phenotype. The clinical outcomes of diseases can be improved by targeted therapy based on the eosinophilic phenotype of asthma and COPD. Dotted and solid lines depict the time course of clinical outcomes, such as the pulmonary function decline, exacerbations, mortality, and treatment response, by each strategy. Dotted lines: Eosinophils target therapy in eosinophilic phenotype of asthma and COPD, Solid lines: No eosinophils target therapy in eosinophilic phenotype of asthma and COPD.

tory biomarkers in asthma and COPD (Fig. 2A). Therefore, the measurement of blood eosinophils may help improve medical efficiency in the management of asthma and COPD (Fig. 2B).

The authors state that they have no Conflict of Interest (COI).

References

1. Brightling CE, McKenna S, Hargadon B, et al. Sputum eosinophilia and the short term response to inhaled mometasone in chronic obstructive pulmonary disease. Thorax **60**: 193-198, 2005.
2. Ortega H, Katz L, Gunsoy N, Keene O, Yancey S. Blood eosinophil counts predict treatment response in patients with severe eosinophilic asthma. J Allergy Clin Immunol **136**: 825-826, 2015.
3. Fowler SJ, Tavernier G, Niven R. High blood eosinophil counts predict sputum eosinophilia in patients with severe asthma. J Allergy Clin Immunol **135**: 822-824 e822, 2015.
4. Negewo NA, McDonald VM, Baines KJ, et al. Peripheral blood eosinophils: a surrogate marker for airway eosinophilia in stable COPD. Int J Chron Obstruct Pulmon Dis **11**: 1495-1504, 2016.
5. McGrath KW, Icitovic N, Boushey HA, et al.; Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute. A large subgroup of mild-to-moderate asthma is persistently noneosinophilic. Am J Respir Crit Care Med **185**: 612-619, 2012.
6. Zhang XY, Simpson JL, Powell H, et al. Full blood count parameters for the detection of asthma inflammatory phenotypes. Clin Exp Allergy **44**: 1137-1145, 2014.
7. Bafadhel M, Greening NJ, Harvey-Dunstan TC, et al. Blood eosinophils and outcomes in severe hospitalized exacerbations of COPD. Chest **150**: 320-328, 2016.
8. Barnes PJ. The cytokine network in asthma and chronic obstructive pulmonary disease. J Clin Invest **118**: 3546-3556, 2008.
9. Jacobsen EA, Jackson DJ, Heffler E, et al. Eosinophil knockout humans: uncovering the role of eosinophils through eosinophil-directed biological therapies. Annu Rev Immunol **39**: 719-757, 2021.
10. Hirano T, Matsunaga K. Late-onset asthma: current perspectives. J Asthma Allergy **11**: 19-27, 2018.
11. Landis SH, Suruki R, Hilton E, Compton C, Galwey NW. Stability of blood eosinophil count in patients with COPD in the UK clinical practice research datalink. COPD **14**: 382-388, 2017.
12. Hartl S, Breyer MK, Burghuber OC, et al. Blood eosinophil count in the general population: typical values and potential confounders. Eur Respir J **55**: 1901874, 2020.
13. Kwon N, Pizzichini E, Bansal AT, et al. Factors that affect blood eosinophil counts in a non-asthmatic population: post hoc analysis of data from Brazil. World Allergy Organ J **13**: 100119, 2020.
14. Benson VS, Hartl S, Barnes N, Galwey N, Van Dyke MK, Kwon N. Blood eosinophil counts in the general population and airways disease: a comprehensive review and meta-analysis. Eur Respir J **59**: 2004590, 2021.
15. Caspard H, Ambrose CS, Tran TN, Chipps BE, Zeiger RS. Associations between individual characteristics and blood eosinophil counts in adults with asthma or COPD. J Allergy Clin Immunol Pract **8**: 1606-1613 e1601, 2020.
16. Shrestha Palikhe N, Bosonea AM, Laratta C, et al. Stability of peripheral blood immune markers in patients with asthma. Allergy Asthma Clin Immunol **15**: 30, 2019.
17. Citgez E, van der Palen J, van der Valk P, Kerstjens HAM, Brusse-Keizer M. Stability in eosinophil categorisation during subsequent severe exacerbations of COPD. BMJ Open Respir Res **8**: e000960, 2021.
18. Wagener AH, de Nijs SB, Lutter R, et al. External validation of

blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. Thorax **70**: 115-120, 2015.
19. Backman H, Lindberg A, Hedman L, et al. FEV1 decline in relation to blood eosinophils and neutrophils in a population-based asthma cohort. World Allergy Organ J **13**: 100110, 2020.
20. Tan WC, Bourbeau J, Nadeau G, et al. High eosinophil counts predict decline in FEV_1: results from the CanCOLD study. Eur Respir J **57**: 2000838, 2021.
21. Hancox RJ, Pavord ID, Sears MR. Associations between blood eosinophils and decline in lung function among adults with and without asthma. Eur Respir J **51**: 1702536, 2018.
22. Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. Lancet Respir Med **3**: 849-858, 2015.
23. Soma T, Iemura H, Naito E, et al. Implication of fraction of exhaled nitric oxide and blood eosinophil count in severe asthma. Allergol Int **67S**: S3-S11, 2018.
24. Bafadhel M, McKenna S, Terry S, et al. Acute exacerbations of chronic obstructive pulmonary disease: identification of biologic clusters and their biomarkers. Am J Respir Crit Care Med **184**: 662-671, 2011.
25. Bafadhel M, McKenna S, Terry S, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med **186**: 48-55, 2012.
26. Ali Z, Dirks CG, Ulrik CS. Long-term mortality among adults with asthma: a 25-year follow-up of 1,075 outpatients with asthma. Chest **143**: 1649-1655, 2013.
27. Suzuki M, Makita H, Konno S, et al.; Hokkaido CCSI. Asthma-like features and clinical course of chronic obstructive pulmonary disease. An analysis from the Hokkaido COPD cohort study. Am J Respir Crit Care Med **194**: 1358-1365, 2016.
28. Casanova C, Celli BR, de-Torres JP, et al. Prevalence of persistent blood eosinophilia: relation to outcomes in patients with COPD. Eur Respir J **50**: 1701162, 2017.
29. Viinanen A, Lassenius MI, Toppila I, et al. The burden of adult asthma in Finland: impact of disease severity and eosinophil count on health care resource utilization. J Asthma **57**: 1092-1102, 2020.
30. Agusti A, Bafadhel M, Beasley R, et al. Precision medicine in airway diseases: moving to clinical practice. Eur Respir J **50**: 1701655, 2017.
31. Leigh R, Pizzichini MM, Morris MM, Maltais F, Hargreave FE, Pizzichini E. Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. Eur Respir J **27**: 964-971, 2006.
32. David B, Bafadhel M, Koenderman L, De Soyza A. Eosinophilic inflammation in COPD: from an inflammatory marker to a treatable trait. Thorax **76**: 188-195, 2021.
33. Watz H, Tetzlaff K, Wouters EF, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respir Med **4**: 390-398, 2016.
34. Calverley PM, Tetzlaff K, Vogelmeier C, et al. Eosinophilia, frequent exacerbations, and steroid response in chronic obstructive pulmonary disease. Am J Respir Crit Care Med **196**: 1219-1221, 2017.
35. Bafadhel M, Peterson S, De Blas MA, et al. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med **6**: 117-126, 2018.
36. Rhyou HI, Nam YH. Predictive factors of response to inhaled corticosteroids in newly diagnosed asthma: a real-world observational study. Ann Allergy Asthma Immunol **125**: 177-181, 2020.
37. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. Thorax **71**: 118-125, 2016.
38. Oishi K, Hirano T, Suetake R, et al. A trial of oral corticosteroids for persistent systemic and airway inflammation in severe asthma. Immun Inflamm Dis **5**: 261-264, 2017.
39. Yamaji Y, Oishi K, Hamada K, et al. Detection of type2 biomarkers for response in COPD. J Breath Res **14**: 026007, 2020.
40. Demarche SF, Schleich FN, Henket MA, Paulus VA, Van Hees TJ, Louis RE. Effectiveness of inhaled corticosteroids in real life on clinical outcomes, sputum cells and systemic inflammation in asthmatics: a retrospective cohort study in a secondary care centre. BMJ Open **7**: e018186, 2017.
41. Deykin A, Lazarus SC, Fahy JV, et al.; Asthma Clinical Research Network, National Heart, Lung, and Blood Institute. Sputum eosinophil counts predict asthma control after discontinuation of inhaled corticosteroids. J Allergy Clin Immunol **115**: 720-727, 2005.
42. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. Eur Respir J **47**: 410-419, 2016.
43. Global Initiative for Chronic Obstructive Lung Disease. 2021 [Internet]. [cited 2021 Dec 27]. Available from: https://goldcopd.org/.
44. Martinez-Garcia MA, Faner R, Oscullo G, et al. Inhaled steroids, circulating eosinophils, chronic airway infection, and pneumonia risk in chronic obstructive pulmonary disease. a network analysis. Am J Respir Crit Care Med **201**: 1078-1085, 2020.
45. Ortega HG, Yancey SW, Mayer B, et al. Severe eosinophilic asthma treated with mepolizumab stratified by baseline eosinophil thresholds: a secondary analysis of the DREAM and MENSA studies. Lancet Respir Med **4**: 549-556, 2016.
46. Kavanagh JE, Hearn AP, Dhariwal J, et al. Real-world effectiveness of benralizumab in severe eosinophilic asthma. Chest **159**: 496-506, 2021.
47. FitzGerald JM, Bleecker ER, Menzies-Gow A, et al. Predictors of enhanced response with benralizumab for patients with severe asthma: pooled analysis of the SIROCCO and CALIMA studies. Lancet Respir Med **6**: 51-64, 2018.
48. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. N Engl J Med **376**: 2448-2458, 2017.
49. Mesnil C, Raulier S, Paulissen G, et al. Lung-resident eosinophils represent a distinct regulatory eosinophil subset. J Clin Invest **126**: 3279-3295, 2016.
50. Ueki S, Konno Y, Takeda M, et al. Eosinophil extracellular trap cell death-derived DNA traps: their presence in secretions and functional attributes. J Allergy Clin Immunol **137**: 258-267, 2016.
51. Ueki S, Tokunaga T, Melo RCN, et al. Charcot-Leyden crystal formation is closely associated with eosinophil extracellular trap cell death. Blood **132**: 2183-2187, 2018.
52. Persson EK, Verstraete K, Heyndrickx I, et al. Protein crystallization promotes type 2 immunity and is reversible by antibody treatment. Science **364**: eaaw4295, 2019.