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Editorial

Discovering Biomarkers of Neutrophilic Asthma: A Clinician's Perspective

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Although asthma is a disease characterized by chronic airway inflammation, for decades, its diagnosis has been through physiological assessment, such as detection of airway hyperresponsiveness or reversible obstruction. Unfortunately, the physiological diagnosis is often not precise and does not directly inform the choice of treatment. It has not been long that a pathological assessment, such as detection of inflammatory markers, was incorporated into asthma management. It is now widely accepted that asthma is a clinical syndrome with various phenotypes and endotypes, and the treatment ideally needs to be determined by inflammatory biomarkers and phenotype stratification.[1] The pathological diagnosis would be a key to successful management, especially for patients with treatment-refractory or severe asthma, as shown in the early clinical trials with mepolizumab.[2,3]

The introduction of T2-biomarkers and novel biologicals is the second breakthrough in the history of asthma management, after anti-inflammatory inhalers (inhaled corticosteroids). T2-targeted biologics are helpful in T2-high severe asthma, not only in controlling asthma symptoms and attacks in the affected individuals but also in reducing future risks of the disease- and oral steroid-related complications.[4] However, there is a sizable proportion of patients without T2 inflammation or even with elevated neutrophils in the airways (sputum neutrophilia of ≥ 61%–65%). Although there is a controversy over the clinical relevance of "being neutrophilic",[5] patients with neutrophilic asthma, comprise approximately 20%–30% of all asthma cases in adults. They are older, comprising more males, and frequently present with more late-onset, severe, or steroid-resistant asthma.[6,7] Thus, the identification and treatment of severe non-T2 asthma remains an area with major unmet needs.[8]

In this issue of *Allergy, Asthma & Immunology Research*, Bich *et al.*[9] investigated human samples and experimental models to test if serum amyloid A1 (SAA1) is a potential biomarker for neutrophilic asthma. They recruited asthmatic patients and healthy controls and found that the serum levels of SAA1 were higher in neutrophilic asthmatic patients (n = 78; 2.7 ± 0.3 ng/mL) than in non-asthmatic controls (n = 60; 2.4 ± 0.2 ng/mL) or non-neutrophilic asthmatic patients (n = 44; 2.3 ± 0.5 ng/mL). Asthmatic patients with high serum SAA1 levels (≥ 2.6 ng/mL) had significantly lower forced expiratory volume in 1 second (% of predicted) (81.4 ± 20.5% vs. 89.4 ± 14.3%; $P = 0.018$), more severe asthma (45% vs. 27%; $P = 0.008$), and higher sputum neutrophil counts (77.3 ± 28.0% vs. 61.8 ± 34.7%; $P = 0.031$), than those with low-SAA1 levels (< 2.6 ng/mL), suggesting the potential relevance of SAA1 in severe neutrophilic

asthma. Furthermore, the authors demonstrated the mechanistic plausibility of SAA1 present in neutrophilic airway inflammation particularly induced by viral infections, using different *in vitro* and *in vivo* asthma models with polyinosinic:polycytidylic acid. SAA1 treatment led to the activation of neutrophils and macrophages isolated from peripheral blood, with the formation of neutrophil extracellular traps and secretion of proinflammatory cytokines presenting M1 phenotype of macrophages.

This work not only suggests a potential biomarker for severe neutrophilic asthma but also explores the mechanistic plausibility of SAA1 in detail.[9] SAA1 is an acute phase protein, blood levels of which are elevated during infection, trauma, surgery, burns, tissue infarction, inflammation, neoplasia, and stress.[10] A significant relationship between serum SAA1 levels and asthma prevalence has been suggested previously.[11,12] Serum SAA1 levels are also elevated in patients with acute exacerbation of chronic obstructive pulmonary disease with neutrophilic inflammation.[13] More recently, it was suggested that SAA1 could bind to house dust mite allergens, driving type 2 responses via inducing the production of interleukin (IL)-33 by airway epithelial cells *in vitro*.[14] The current study by Bich *et al.*[9] broadened the knowledge on SAA1 in asthma, and added the details of SAA1 that are specific to the pathogenesis of neutrophilic asthma, particularly induced by viral infection.

In this editorial, however, we would like to appraise the findings and raise questions from a clinician's perspective. First, at least presently, neutrophilic inflammation is not being assessed in usual clinical practice because it does not inform treatment decision. The absence of T2 (or eosinophilic) inflammation is a useful guide in clinical decision-making, but it does not indicate that the presence of neutrophilic inflammation is clinically relevant. Moreover, clinical trials with brodalumab (anti-IL-17 receptor antibody), golimumab (anti-tumor necrosis factor-α antibody), and AZD5069 (CXCR2 receptor antagonist) failed to show significant improvements over placebos, in patients with moderate or severe asthma.[15-17] Treatment with risankizumab, blocking the p19 subunit of IL-23, was rather associated with worse clinical outcomes in severe asthmatic patients compared with those treated with placebo, although it led to the downregulated expression of sputum genes involved in the activation of natural killer and cytotoxic T cells and the activation of type 1 helper T and type 17 helper T transcription factors.[18]

Secondly, owing to the nature of neutrophils as acute phase reactant to microbial or pollutant exposure,[19,20] it is uncertain if neutrophilic asthma is a stable phenotype in individuals. Neutrophilic inflammation is also confounded by oral corticosteroid treatments in severe asthmatic patients, as steroids can prolong neutrophil survival and prevent apoptosis.[21] In this regard, a question is raised: a simple counting of neutrophil numbers in sputum is not precise enough to define a "clinically relevant" phenotype of neutrophilic asthma? Neutrophil activation markers may be more useful than cell number quantitation, although the former is technically more challenging.[22] These indicate the limitations of current phenotyping approaches and emphasize the need for endotype research to precisely define neutrophilic or non-T2 asthma as well as discover its biomarkers and treatment targets. The integration of clinical trials with omics analyses may help reveal novel pathways and biomarkers.[23] As there are multiple pathways leading to neutrophilic inflammation,[20,24] the key mechanisms are likely heterogeneous across different disease context (or depending on triggers); thus, the experimental works by Bich *et al.*[9] are relevant in that they evaluated the roles of SAA1 in virus-induced neutrophilic asthma.

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Thirdly, the clinical utility of SAA1 as a biomarker needs to be validated. Given the multi-faceted nature of neutrophilic inflammation, participants should be further characterized based on exacerbation status, viral infection, and oral steroid use. Diagnostic utility, usually assessed with area under the curve analyses, was not presented in this study.[9] Also, the degree of diagnostic precision is not clear from the data in Table 2,[9] as sputum neutrophilia was not infrequent even in the low-SAA1 group. Although serum SAA1 levels were significantly higher in neutrophilic asthmatic patients than in the compared groups, the levels were not different between non-asthmatic controls and non-neutrophilic asthmatic patients (Table 1),[9] indicating that SAA1 is a broad marker of systemic neutrophilic inflammation rather than asthma-specific. Comorbidities that may confound serum levels of SAA1 should also be explored and controlled in further validation studies. The diagnostic utility should be confirmed in external cohorts and compared with other biomarkers previously reported for neutrophilic asthma.

Despite the prevailing questions, the work by Bich *et al.*[9] is a welcoming addition, contributing to high hopes in the search of neutrophilic asthma biomarkers. Neutrophilic asthma has major unmet needs, and further understanding as to why neutrophil numbers are increased in asthmatic airways will facilitate the development of biomarkers and help develop precision therapies for severe asthmatic patients who are not responsive to T2-targeted biologics. These advances would be the next breakthrough in asthma management.

REFERENCES

1. Lee Y, Quoc QL, Park HS. Biomarkers for severe asthma: lessons from longitudinal cohort studies. Allergy Asthma Immunol Res 2021;13:375-89.
PUBMED | CROSSREF
2. Flood-Page P, Swenson C, Faiferman I, Matthews J, Williams M, Brannick L, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. Am J Respir Crit Care Med 2007;176:1062-71.
PUBMED | CROSSREF
3. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. Lancet 2012;380:651-9.
PUBMED | CROSSREF
4. Song WJ, Lee JH, Kang Y, Joung WJ, Chung KF. Future risks in patients with severe asthma. Allergy Asthma Immunol Res 2019;11:763-78.
PUBMED | CROSSREF
5. Nair P, Surette MG, Virchow JC. Neutrophilic asthma: misconception or misnomer? Lancet Respir Med 2021;9:441-3.
PUBMED | CROSSREF
6. Sur S, Crotty TB, Kephart GM, Hyma BA, Colby TV, Reed CE, et al. Sudden-onset fatal asthma. A distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? Am Rev Respir Dis 1993;148:713-9.
PUBMED | CROSSREF
7. Moore WC, Hastie AT, Li X, Li H, Busse WW, Jarjour NN, et al. Sputum neutrophil counts are associated with more severe asthma phenotypes using cluster analysis. J Allergy Clin Immunol 2014;133:1557-1563.e5.
PUBMED | CROSSREF
8. Kyriakopoulos C, Gogali A, Bartziokas K, Kostikas K. Identification and treatment of T2-low asthma in the era of biologics. ERJ Open Res 2021;7:00309-02020.
PUBMED | CROSSREF
9. Bich TCT, Quoc QL, Choi Y, Yang EM, Trinh HKT, Shin YS, et al. Serum amyloid a1: a biomarker for neutrophilic airway inflammation in adult asthmatic patients. Allergy Asthma Immunol Res 2022;14:40-58.
CROSSREF
10. Jensen LE, Whitehead AS. Regulation of serum amyloid A protein expression during the acute-phase response. Biochem J 1998;334:489-503.
PUBMED | CROSSREF

11. Jousilahti P, Salomaa V, Hakala K, Rasi V, Vahtera E, Palosuo T. The association of sensitive systemic inflammation markers with bronchial asthma. Ann Allergy Asthma Immunol 2002;89:381-5.
PUBMED | CROSSREF

12. Ozseker F, Buyukozturk S, Depboylu B, Yilmazbayhan D, Karayigit E, Gelincik A, et al. Serum amyloid A (SAA) in induced sputum of asthmatics: a new look to an old marker. Int Immunopharmacol 2006;6:1569-76.
PUBMED | CROSSREF

13. Bozinovski S, Uddin M, Vlahos R, Thompson M, McQualter JL, Merritt AS, et al. Serum amyloid A opposes lipoxin A_4 to mediate glucocorticoid refractory lung inflammation in chronic obstructive pulmonary disease. Proc Natl Acad Sci U S A 2012;109:935-40.
PUBMED | CROSSREF

14. Smole U, Gour N, Phelan J, Hofer G, Köhler C, Kratzer B, et al. Serum amyloid A is a soluble pattern recognition receptor that drives type 2 immunity. Nat Immunol 2020;21:756-65.
PUBMED | CROSSREF

15. Busse WW, Holgate S, Kerwin E, Chon Y, Feng J, Lin J, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. Am J Respir Crit Care Med 2013;188:1294-302.
PUBMED | CROSSREF

16. Wenzel SE, Barnes PJ, Bleecker ER, Bousquet J, Busse W, Dahlén SE, et al. A randomized, double-blind, placebo-controlled study of tumor necrosis factor-alpha blockade in severe persistent asthma. Am J Respir Crit Care Med 2009;179:549-58.
PUBMED | CROSSREF

17. O'Byrne PM, Metev H, Puu M, Richter K, Keen C, Uddin M, et al. Efficacy and safety of a CXCR2 antagonist, AZD5069, in patients with uncontrolled persistent asthma: a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2016;4:797-806.
PUBMED | CROSSREF

18. Brightling CE, Nair P, Cousins DJ, Louis R, Singh D. Risankizumab in severe asthma - a phase 2a, placebo-controlled trial. N Engl J Med 2021;385:1669-79.
PUBMED | CROSSREF

19. Son JH, Kim JH, Chang HS, Park JS, Park CS. Relationship of microbial profile with airway immune response in eosinophilic or neutrophilic inflammation of asthmatics. Allergy Asthma Immunol Res 2020;12:412-29.
PUBMED | CROSSREF

20. Crisford H, Sapey E, Rogers GB, Taylor S, Nagakumar P, Lokwani R, et al. Neutrophils in asthma: the good, the bad and the bacteria. Thorax 2021;76:835-44.
PUBMED | CROSSREF

21. Cox G. Glucocorticoid treatment inhibits apoptosis in human neutrophils. Separation of survival and activation outcomes. J Immunol 1995;154:4719-25.
PUBMED

22. Kim SH, Uuganbayar U, Trinh HKT, Pham DL, Kim N, Kim M, et al. Evaluation of neutrophil activation status according to the phenotypes of adult asthma. Allergy Asthma Immunol Res 2019;11:381-93.
PUBMED | CROSSREF

23. Badi YE, Pavel AB, Pavlidis S, Riley JH, Bates S, Kermani NZ, et al. Mapping atopic dermatitis and anti-IL-22 response signatures to type 2-low severe neutrophilic asthma. J Allergy Clin Immunol. Forthcoming 2021.
PUBMED | CROSSREF

24. Hynes GM, Hinks TSC. The role of interleukin-17 in asthma: a protective response? ERJ Open Res 2020;6:00364-02019.
PUBMED | CROSSREF