Granulocytic Airway Inflammation and Clinical Asthma Outcomes

Prospective longitudinal studies looking at the relationship between airway inflammation and clinical asthma outcomes in real life are of great importance to better understand the disease and choose appropriate treatment. The Severe Asthma Research Program III (SARP III) is a network of U.S. investigators whose purpose is to advance the understanding of severe asthma through integration of mechanistic studies with detailed phenotypic and endotypic characterization (1).

In this issue of the *Journal*, Hastie and colleagues (pp. 882–892) report on the stability/instability of airway granulocytic inflammation by analyzing induced sputum cell content over a 3-year period and relate granulocytic inflammation to clinical outcomes such as exacerbation, day-to-day asthma control, and lung function decline in 206 subjects with asthma, the large majority of whom were on inhaled corticosteroids (ICS)/long-acting β_2-agonists as maintenance treatment (2). Treatment change was left at the discretion of the investigators, but initiation of any biologics led to exclusion of the patients. In their article, Hastie and colleagues proposed two patient group classifications. One was based on sputum eosinophil or neutrophil count variability, identifying three groups as predominant low, highly variable, and predominant high. The other was based on the combination of low/high sputum eosinophil and neutrophil, leading to four groups called paucigranulocytic, neutrophilic, eosinophilic, or mixed granulocytic, as defined by Simpson and colleagues (3). The current study brings several key results. The first important finding is that the predominant low eosinophil group is the largest, representing 59% of the patients enrolled, whereas the highly variable and predominant high groups accounted for 15% and 25%, respectively. Therefore, most of the patients display a relative stability in their eosinophilic phenotype over the follow-up. The proportion of the predominant low eosinophil group may appear surprisingly high in this study, which mainly focused on severe asthma compared with a previous severe asthma cohort study (4), but it may be overestimated because the authors have excluded patients using biologics. However, recent real-world data have shown that anti–IL-5 and omalizumab are generally administrated in patients with significant increases in sputum eosinophils (5, 6).

Second, the predominant low eosinophil group shows the highest baseline lung function, no disease progression as reflected by change in FEV_1, and the lowest exacerbation rate. The highly variable group shows reduced expiratory flow rates with greater airway obstruction, higher reversibility to albuterol, and the highest rate of exacerbation despite a higher use of ICS/long-acting β_2-agonists and leukotriene receptor antagonists (Figure 1). The predominant high eosinophil group shows equally altered expiratory flow rate, airway obstruction, and reversibility as the highly variable group but with a lower rate of healthcare use, which is actually comparable to the predominant low eosinophil group. Adopting similar classification with sputum neutrophils does not reveal any relevant disease characteristics apart from older age in those in the predominant high neutrophil group, which is confirmatory of previous findings (7). The results of the current study (2) further support the role of fluctuation of sputum eosinophil count in modifying asthma control as it has been highlighted by Demarche and colleagues (8) in a real-life study in which fluctuation in Asthma Control Questionnaire six-item version was partly and independently determined by fluctuation in sputum eosinophils and FEV_1. In Hastie's study, the exacerbation rate was greater in the group with high sputum eosinophil variation than in the group with persistently high count, indicating that a temporary rise in sputum eosinophils may be a factor for asthma exacerbation; this finding is in agreement with the strategy of maintaining a low level of sputum eosinophils to reduce exacerbation (9). The current study (2) clearly demonstrates, however, that exacerbation may happen in those patients with predominant low sputum eosinophils, and other SARP III publications have shown that high plasma IL-6 concentrations, which are associated with blood neutrophilia and metabolic dysfunction and obesity (10), were predictive of exacerbation (11). It is worth noting that the group with high sputum neutrophil count variation was not at greater risk of exacerbation, as opposed to the group with high eosinophil fluctuation.

Third, in addition to asthma control and exacerbation rate, the current study also looked at pre- and post-bronchodilation FEV_1 decline over 3 years. Overall, the changes in pre- and post-bronchodilation FEV_1 were very limited and the predominantly low and highly variable eosinophil groups even displayed a small increase of 1–2% in pre- and post-bronchodilation FEV_1% predicted after 3 years. The airway inflammatory pattern that was associated with the greater loss in lung function was characterized by persistent eosinophil-high and neutrophil high-infiltrate, which is called mixed granulocytic asthma. This phenotype was previously associated with the most altered lung function in another large cross-sectional study (7) (Figure 1). Hastie and colleagues found an average loss in post-bronchodilation FEV_1 between 1% and 2% predicted after 3 years. By contrast, neither the isolated predominant high sputum eosinophil group nor the isolated predominant high sputum neutrophil group displayed such a loss in lung function. This would therefore suggest that it is the interaction between eosinophils and neutrophils that enhances the potential of airway remodeling, assuming that the latter is reflected by progressive decline in FEV_1. There are *in vitro* studies that support a role for neutrophils directly or indirectly enhancing eosinophil function, with neutrophil elastase favoring eosinophil degranulation (12) and maturation of IL-33 (13), a potent agonist for eosinophils. Moreover, there is *in vivo* evidence that airway neutrophils may prevent ICS from delivering beneficial effects in asthma (14). In another longitudinal study, the group with persistent high eosinophilic airway inflammation did not show

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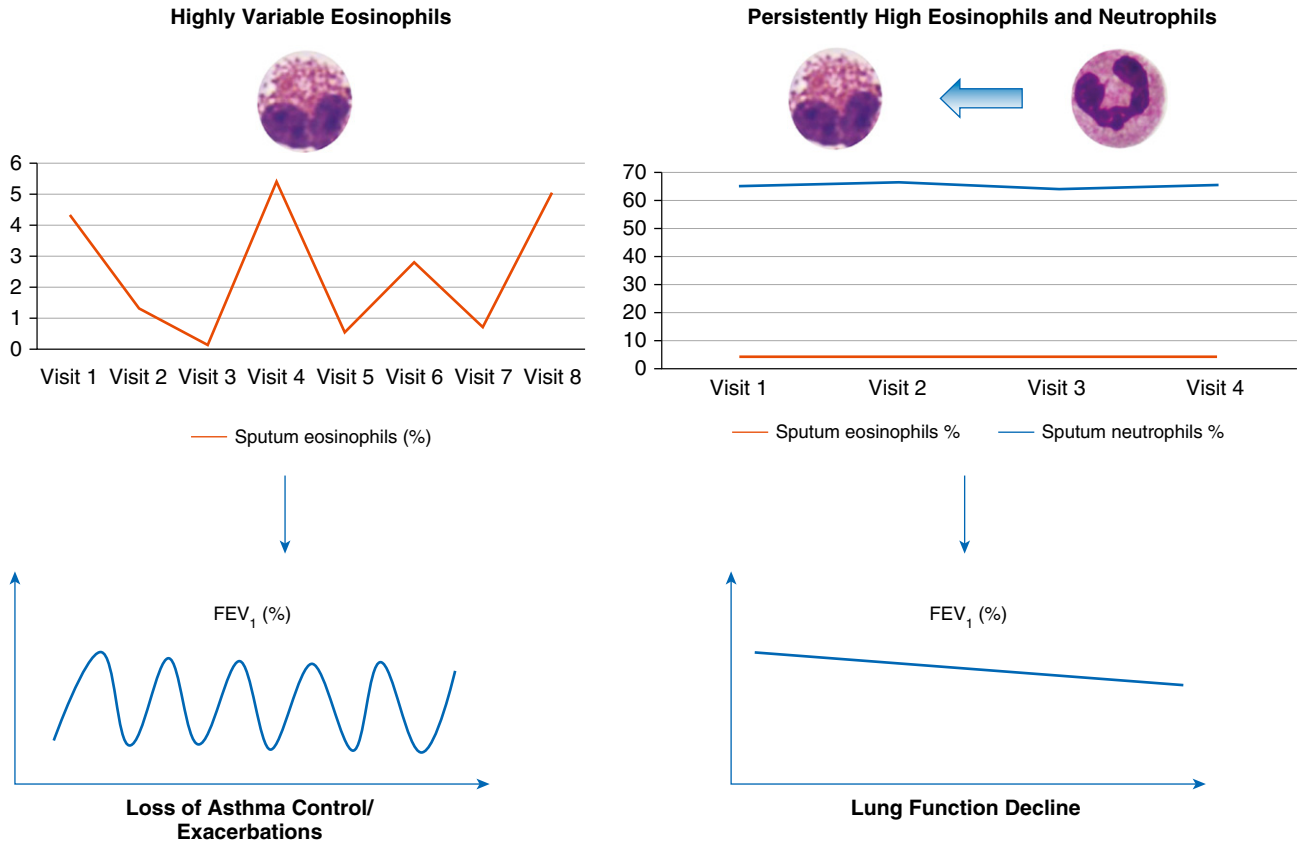

Figure 1. Relationship between granulocytic airway pattern and asthma clinical outcomes. The arrow in the top right panel indicates that neutrophils may enhance eosinophil degranulation.

accelerated lung function decline but had lower sputum neutrophil counts than the fast decliner group with highly variable sputum eosinophils (4), further supporting the idea that the combination of eosinophils and neutrophils is important in lung function decline. On the other hand, the current study by Hastie and colleagues show that healthcare use in mixed granulocytic asthma was, however, not strikingly different from that seen in other groups, illustrating that processes leading to progressive lung function decline may be different from the ones resulting in loss of control and exacerbation. Whether biologics, which are potent at reducing exacerbation rates in subjects with T2 severe asthma, may actually prevent the loss of lung function in those with mixed granulocytic asthma remains to be clarified in long-term longitudinal studies.

Finally, it is worth noting that, whichever classification is chosen, the patients in SARP III show, over 3 years of follow-up, an improvement in asthma control together with consistent reduction in exacerbation, which may even approach 60% in the predominant eosinophil low group (2). It is even more remarkable that, over the same duration, the proportion of patients with high-dose ICS was reduced, thereby pointing to an overdosing of ICS in real life in many patients with asthma. There is no doubt that improved drug adherence linked to study participation may have contributed to this observation, but we might not exclude that a reduction in the dosage of ICS may really be beneficial to some patients, especially in the groups without high sputum eosinophil counts. Recent studies focusing on noneosinophilic or non-T2 asthma have shown maintained or improved asthma control in some patients when stepping down ICS (15, 16). As advocated by Beasley and colleagues (17), it is time to set a new target for asthma: for patients with uncontrolled asthma, we should consider underlying inflammatory phenotypes and associated comorbid traits before initiating any systematic step-up in ICS dose. ■

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Renaud E. Louis, M.D., Ph.D.
Florence N. Schleich, M.D., Ph.D.
Department of Pneumology
CHU Liege
Liege, Belgium

References

1. Teague WG, Phillips BR, Fahy JV, Wenzel SE, Fitzpatrick AM, Moore WC, *et al*. Baseline features of the Severe Asthma Research Program (SARP III) cohort: differences with age. *J Allergy Clin Immunol Pract* 2018;6:545–554.e4.
2. Hastie AT, Mauger DT, Denlinger LC, Coverstone A, Castro M, Erzurum S, *et al*. Mixed sputum granulocyte longitudinal impact on lung function in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2021;203:882–892.

3. Simpson JL, Scott R, Boyle MJ, Gibson PG. Inflammatory subtypes in asthma: assessment and identification using induced sputum. *Respirology* 2006;11:54–61.
4. Newby C, Agbetile J, Hargadon B, Monteiro W, Green R, Pavord I, *et al*. Lung function decline and variable airway inflammatory pattern: longitudinal analysis of severe asthma. *J Allergy Clin Immunol* 2014; 134:287–294.
5. Frix AN, Schleich F, Paulus V, Guissard F, Henket M, Louis R. Effectiveness of omalizumab on patient reported outcomes, lung function, and inflammatory markers in severe allergic asthma. *Biochem Pharmacol* 2020;179:113944.
6. Schleich F, Graff S, Nekoee H, Moermans C, Henket M, Sanchez C, *et al*. Real-word experience with mepolizumab: does it deliver what it has promised? *Clin Exp Allergy* 2020;50:687–695.
7. Schleich FN, Manise M, Sele J, Henket M, Seidel L, Louis R. Distribution of sputum cellular phenotype in a large asthma cohort: predicting factors for eosinophilic vs neutrophilic inflammation. *BMC Pulm Med* 2013;13:11.
8. Demarche SF, Schleich FN, Paulus VA, Henket MA, Van Hees TJ, Louis RE. Asthma control and sputum eosinophils: a longitudinal study in daily practice. *J Allergy Clin Immunol Pract* 2017;5: 1335–1343.e5.
9. Green RH, Brightling CE, McKenna S, Hargadon B, Parker D, Bradding P, *et al*. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360: 1715–1721.
10. Peters MC, McGrath KW, Hawkins GA, Hastie AT, Levy BD, Israel E, *et al*.; National Heart, Lung, and Blood Institute Severe Asthma Research Program. Plasma interleukin-6 concentrations, metabolic dysfunction, and asthma severity: a cross-sectional analysis of two cohorts. *Lancet Respir Med* 2016;4:574–584.
11. Peters MC, Mauger D, Ross KR, Phillips B, Gaston B, Cardet JC, *et al*. Evidence for exacerbation-prone asthma and predictive biomarkers of exacerbation frequency. *Am J Respir Crit Care Med* 2020;202: 973–982.
12. Liu H, Lazarus SC, Caughey GH, Fahy JV. Neutrophil elastase and elastase-rich cystic fibrosis sputum degranulate human eosinophils in vitro. *Am J Physiol* 1999;276:L28–L34.
13. Lefrançais E, Roga S, Gautier V, Gonzalez-de-Peredo A, Monsarrat B, Girard JP, *et al*. IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G. *Proc Natl Acad Sci USA* 2012; 109:1673–1678.
14. Green RH, Brightling CE, Woltmann G, Parker D, Wardlaw AJ, Pavord ID. Analysis of induced sputum in adults with asthma: identification of subgroup with isolated sputum neutrophilia and poor response to inhaled corticosteroids. *Thorax* 2002;57:875–879.
15. Demarche S, Schleich F, Henket M, Paulus V, Louis R, Van Hees T. Step-down of inhaled corticosteroids in non-eosinophilic asthma: a prospective trial in real life. *Clin Exp Allergy* 2018;48:525–535.
16. Heaney LG, Busby J, Hanratty CE, Djukanovic R, Woodcock A, Walker SM, *et al*.; investigators for the MRC Refractory Asthma Stratification Programme. Composite type-2 biomarker strategy versus a symptom-risk-based algorithm to adjust corticosteroid dose in patients with severe asthma: a multicentre, single-blind, parallel group, randomised controlled trial. *Lancet Respir Med* 2021;9: 57–68.
17. Beasley R, Braithwaite I, Semprini A, Kearns C, Weatherall M, Pavord ID. Optimal asthma control: time for a new target. *Am J Respir Crit Care Med* 2020;201:1480–1487.

Asthma and COVID-19: Preconceptions about Predisposition

It is now just past 15 months since coronavirus disease (COVID-19) was identified in China and rapidly spread throughout the world. There has been an extraordinary research effort to understand the pathophysiology of COVID-19, providing an evidence base on which to develop public health, therapeutic, and vaccine interventions. The burden of COVID-19 falls disproportionately on different populations, and research has sought to rapidly identify those at higher risk, such as those with specific comorbidities.

The situation with asthma was intriguing from the outset of the pandemic, with initial case series either not reporting that COVID-19 infections provoked severe exacerbations of asthma (1, 2) or specifically reporting that patients hospitalized with COVID-19 did not present with severe asthma exacerbations (3). These observations were unexpected, as viral respiratory tract infections are the most common cause of severe exacerbations of asthma. Specifically, *Coronaviridae* are associated with up to 13% of asthma exacerbations in children (4) and up to 16% in adults (5).

Whether people with asthma represented a high-risk population came into sharp focus when chronic obstructive pulmonary disease was strongly associated with severe disease, ICU admission, and death (6, 7). However, a similar risk was not identified with asthma when adjusted for other variables, although asthma with recent oral corticosteroid use increased the risk of mortality from COVID-19 in one study (8).

These reports were followed by a systematic review and meta-analysis of COVID-19 studies that reported outcomes in patients with asthma and had been published by August 18, 2020 (9). The main findings of this review were that asthma was not associated with higher COVID-19 severity and that patients with asthma had a lower risk of death. Knowledge in this field has now been extended with the publication by Terry and colleagues (pp. 893–905) of a systematic review and meta-analysis of studies in this issue of the *Journal* that examined the prevalence and/or risk of severe disease in adult patients with asthma and COVID-19 (10). Advantages of this current review include the availability of considerably more studies for inclusion in the meta-analysis, the comparison with asthma prevalence rates in the broad populations studied, and the use of multivariate modeling in the subset of studies of asthma and COVID-19 mortality.

First, the authors report that their findings suggest the possibility of a moderate decreased risk of a COVID-19 diagnosis in

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