

Type 2 Biomarkers in Asthma: Yet Another Reflection of Heterogeneity



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Severe type 2 (T2) asthma is not a monolith. New layers of heterogeneity and complexity of asthma continue to be unveiled in both clinical features and mechanistic underpinnings. T2 biomarker signals in severe asthma are no exception. As has been recognized in recent clinical trials of severe asthma, the cardinal T2 biomarkers—blood eosinophil count, sputum eosinophil percentage, fraction of exhaled nitric oxide (FENO), and serum IgE level—do not necessarily perfectly correlate with each other. These biomarkers, particularly the blood-based measurements, are themselves imperfect surrogates for mechanism at the airway level. An individual with severe asthma may have elevation of one T2 biomarker but not of another. Further complexity is introduced when degree of biomarker elevation or differences in cutoff point used are considered. T2 inflammation occurs along a continuum in the airways of patients with asthma, and these patients begin to exhibit specific clinical characteristics after exceeding a threshold of inflammatory cytokine expression.^{1,2} The surrogate markers used to determine underlying inflammation are highly variable and therefore need to be repeated to increase the accuracy of phenotypic characterization.³ This may be related to effects of triggers and therapies on both underlying inflammation and the associated biomarkers. Systematic examinations of the patterns of T2 biomarker elevation in blood eosinophils, FENO, and IgE reflecting data commonly obtained in real-world practice can help inform the heterogeneity that exists within severe T2 asthma.

In this edition of the journal, Frossing et al⁴ describe the prevalence of T2 biomarker patterns and associated clinical characteristics in a cohort of patients with severe asthma

compiled from 2 Danish cross-sectional studies. The authors' work in this publication is supportive of the existing literature that demonstrates a significant amount of heterogeneity in the expression and coexpression of T2 biomarkers in patients with severe asthma. Among the population of patients in this study, 70% demonstrated elevation of at least 1 T2 biomarker, indicating that a large majority of patients with severe asthma have a component of detectable T2 inflammation. Interestingly, a very small proportion (only 15%) of patients demonstrate elevation of all 3 biomarkers including FENO, IgE, and blood eosinophils, though the choice to use a relatively high IgE cutoff point of 150 U/mL did influence this result. The findings presented confirm that the extent to which various T2 pathways are active varies widely from patient to patient and that a relatively small percentage has augmentation of all 3 T2 cytokines. In addition, the prevalence of elevation of each singular biomarker in isolation occurs in about 40% of the population. This highlights the importance of characterizing T2 inflammation in multiple domains and categorizing severe asthma as T2 on the basis of the presence of at least 1 elevated biomarker and not requiring 2 or all 3 markers to be elevated.

There were no significant differences in clinical characteristics in patients who had elevations in all 3 biomarkers as compared with the other groups with elevations in 1 or 2 biomarkers, a surprising result because one would expect this group to have significantly augmented T2 inflammation at the airway level. The study population differed from those in several of the phase III studies for biologics in severe asthma in that the population was less obese, had a very high prevalence of nasal polyps (40% of assessed patients), and had on average fewer exacerbations and higher asthma control questionnaire scores.^{5,6} Therein lies the challenge in attempting to determine the prevalence of specific biomarkers in a population with severe asthma. Not all populations with severe asthma are the same, and there appears to be a spectrum of severity that is required in clinical trials that does not completely mirror unselected populations with severe asthma. Comparisons are therefore challenging. In addition, the threshold selected for assigning elevated status differs among studies, further complicating the ability to make direct comparisons and draw conclusions. International harmonization is required to determine the accepted thresholds applied to the definitions of T2 inflammation to facilitate head-to-head comparisons in the arena of severe asthma clinical research.

Elevated biomarkers may indicate differential inflammatory pathways in each patient. The inherent complexity that denotes the multiple inflammatory pathways that may be activated in a given patient with asthma and whether one is dominant over the others underscores the reason for the various conclusions in studies that aim to determine the association of T2 markers and severe asthma. Atopy (IgE), eosinophilic inflammation (blood

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eosinophils), and IL-13—driven inflammation (FENO) are overlapping but distinct processes. Even within these individual components of T2 inflammation, there is heterogeneity. For instance, a patient with severe asthma with strong eosinophil signals may have eosinophilia driven by IL-5 from T_H2 lymphocytes in the classic T2 paradigm or from other sources, including ILC2 cells.⁷ These 2 pathways may be singular or overlapping, and lumping all eosinophilic patients into one group would likely lead to inaccurate conclusions.

Frossing et al's work highlights the importance of putting biomarkers into clinical context. Understanding whether an elevated IgE is associated with clinical evidence of allergic sensitization for instance and to what extent that level of sensitization is driving asthma exacerbations is essential in determining how to target treatment. Similarly, determining the impact of an elevated FENO or blood eosinophil count on the frequency of exacerbations, asthma control, and quality of life is crucial. T2 disease can occur on a continuum, causing isolated asthma or concomitant diseases in the upper airway, aerodigestive track, or skin. Understanding whether these concomitant diseases are targets of therapy or predictors of response to therapy is important in the context of T2 asthma. The authors attempted to determine the association of T2 comorbidities on the biomarkers of interest and noted associations between elevations in all 3 biomarkers and the presence of nasal polyps. Nasal polyps were more frequently noted when there were elevations in all 3 biomarkers, concomitant IgE and FENO, and concomitant eosinophils and FENO. More work is needed to determine how the various biomarkers intersect with the spectrum of T2 diseases to improve the clinical utility of these markers.

The authors performed sputum cytology in 81% of their combined cohort and found that neutrophilic sputum (24%) is not as common as paucigranulocytic sputum (68%) in those without elevations in any of the T2 biomarkers. Approximately 30% of patients with severe asthma in this study did not exhibit any evidence of T2 inflammation. There is currently a paucity of clear understanding of non-T2 asthma. There is no consensus on the description of this subtype, and it is likely that non-T2 asthma is equally heterogeneous with multiple underlying in-

flammatory mechanisms at play.⁸ The prevalence of non-T2 asthma may also differ in mild to moderate as compared with severe asthma, with some studies demonstrating that nearly two-third of patients with mild to moderate disease have persistent noneosinophilic inflammation.⁹

The goal of providing care in a precise and targeted manner cannot be realized until the tools we use to identify patients are sharpened, and this will likely require the use of advanced techniques to identify and refine asthma endotypes. Endotyping will enable the identification of putative pathways that underlie the inflammatory types that are seen in clinical practice and further our knowledge of how intersecting inflammatory mechanisms drive asthma phenotypes. In addition, moving beyond surrogate markers will allow more specific identification of causative pathways that can be targeted with available biologics in severe disease.

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