Yin and yang of asthmatic inflammatory biomarkers and gene expression

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Persistent asthma is characterized by the presence of reversible airflow obstruction, airway hyperresponsiveness, and symptoms and exacerbations in association with airway inflammation. Measurement of type 2 (T2) biomarkers in patients with poorly controlled asthma is important in defining the particular inflammatory phenotype. In real-life clinical practice, this involves measuring fractional exhaled nitric oxide (FENO), peripheral blood eosinophils (PBEs), and IgE. These biomarkers are commonly used to infer activity of T2 proinflammatory cytokines, namely, IL- 4, IL-5, and IL-13, with PBE being predominantly driven by IL-5, and IgE and FENO by IL-4 and IL-13.[1] Such patients with T2-high asthma usually respond well to corticosteroids and T2 biologics. In contrast, patients with T2-low asthma may have increased expression of IL-17 in association with more neutrophilic inflammation, which tends to be corticosteroid-resistant and less responsive to currently available T2 biologics (Fig 1).

In this issue of the *Journal*, Diver et al[2] have elegantly performed a *post hoc* baseline exploratory analysis of a phase 2 biologic trial in a subgroup of 79 patients with moderate to severe asthma, to delve into the putative relationships of such T2 biomarkers with bronchial epithelial gene signatures. Pointedly, patients who had a history of frequent exacerbations were not included because of the risk associated with bronchoscopy. Three subgroups of patients were identified to be associated with inflammatory epithelial gene clusters, namely, T2-high-T17-low, T17-high-T2-low, and T2-low-T17-low. No T2-high-T17-high participants were observed, but these subjects were possibly excluded with the frequent exacerbator group.

FENO levels were the highest in T2-high-T17-low, lowest in T17-high-T2-low, and intermediate in T2-low-T17-low gene expression. Unsurprisingly, T2-high patients also had higher levels of eosinophils in sputum and bronchial biopsy. CYST-1, which encodes the cysteine protease inhibitor Cystatin SN, was the most upregulated gene, being 34-fold higher in patients with raised versus low FENO levels. Likewise, CYST-1 had the highest expression in patients with raised PBE or IgE. The clinical phenotypes were however not different when comparing between the 3 gene clusters in terms of lung function, asthma control, and exacerbations. The authors acknowledged the limitations in terms of comparisons between gene cluster groups due to sample size constraints as well as excluding frequent exacerbators. Although spirometry was performed to quantify airflow obstruction, notably, there was no assessment of small airways function using oscillometry, for instance, to measure peripheral lung resistance and compliance.[3]

In this respect, we already know from larger patient cohorts that the combination of raised PBE and FENO, the so-called type 2 pivot, is predictive of exacerbations in patients with severe asthma.[4] The presence of comorbidity with nasal polyposis is also associated with higher PBE and FENO levels in patients with more severe asthma.[5] Other data have reported that T17-high patients tend to be leaner male smokers who are more exacerbation prone with accompanying airway neutrophilia.[6]

Where does this leave us with regard to implications for everyday clinical practice? In reality, we are presently not at the stage of performing inflammatory gene profiling from bronchial brushings on a routine basis to stratify exacerbation risk and guide tailored therapy. It would however be pertinent to know whether the same gene expression profiles could be ascertained from nasal brushings in patients with asthma even in the absence of overt upper airway disease, given that nasal brushings are easier to perform in a routine clinic setting.

One key question is how such inflammatory phenotypes relate to asthma therapy. The relationship between PBE and FENO, the bronchial T2-high expression signature, and the dose-response relationship to inhaled corticosteroid is well documented.[7] Responder analysis of phase 3 biologic trials shows that the presence of PBE greater than or equal to 300 cells/μL predicts good response to treatment with anti-IL-5 or anti–IL-5 receptor alpha (Rα), whereas PBE greater than or equal to 300 cells/μL or FENO greater than or equal to 25 parts per billion are both predictive of response to anti–IL-4Rα and anti–thymic stromal lymphoprotein (TSLP), with regard to reducing exacerbations in severe asthma. This is perhaps not surprising given that anti-IL-5 and anti–IL-5Rα act to suppress or deplete PBE, whereas anti–IL-4Rα and anti-TSLP both reduce IL-4/IL-13 signaling and accompanying FENO levels. Large prospective studies are indicated to

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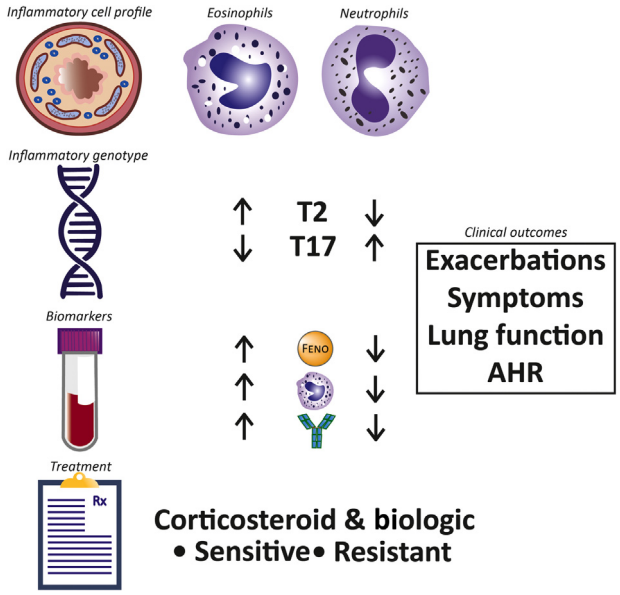

FIG 1. Depiction of common inflammatory cell profiles, genotypes, biomarkers, clinical outcomes, and available treatments for patients with persistent moderate to severe asthma. *AHR*, Airway hyperresponsiveness; *T2/17*, type 2/17 inflammation.

investigate the effects of type 2 biologics in patients with particular T2-high phenotypes rather than relying on *post hoc* exploratory responder analysis. To date, no biologics have demonstrated efficacy in T2-low asthma although the anti-TSLP agent tezepelumab has shown significant reductions in exacerbations albeit in a responder analysis of a phase 3 trial.[1] Whether epithelial gene expression profiling will help to further refine tailored biologic therapy warrants further evaluation.

From the prescriber's perspective, measurement of FENO remains the only available point-of-care biomarker currently recommended in guidelines,[8] the levels of which can also be useful to provide feedback to patients regarding their T2 asthma inflammatory status. Although domiciliary monitoring of FENO is in theory currently available with portable devices, this is not likely to be practical on a wide-scale basis due to prohibitive cost constraints. Having said that, simply ascertaining the asthma control questionnaire by the patient is also a strong predictor of future exacerbation risk,[9] which, along with domiciliary peak flow, can be used to personally adjust treatment. One example of this type of patient-centered regimen is the Global Initiative for Asthma–recommended use of inhaled corticosteroid with formoterol single-inhaler combination as anti-inflammatory reliever and maintenance therapy, which addresses both T2 inflammation and airway smooth muscle stability to improve disease control and reduce exacerbations.[10]

Nonetheless, the main message from guidelines remains clear in terms of including T2 biomarker profiling as part of the routine workup of patients with moderate to severe persistent asthma, along with careful history taking to assess relevant trigger factors. This should be performed in addition to measurement of airflow obstruction with spirometry perhaps in conjunction with oscillometry to assess small airways, as well as imaging to identify airway mucous plugging, wall thickening, and air trapping. When considering the yin and yang of asthmatic inflammation, such comprehensive phenotyping, while time consuming, will in the long run identify treatable traits and lead to optimal patient outcomes for our patients with more severe asthma.

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