Eosinophilia in asthma: the easy way is not always the best

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According to the latest version of the GINA Strategy document[1], asthma is considered a heterogeneous disease with clinical manifestations sustained by different molecular mechanisms; in particular, these manifestations may be (but are not invariably) associated with chronic airway inflammation[1]. Indeed, part of the heterogeneity of asthma may be due to different intensities or patterns (eg eosinophilic vs neutrophilic) of airway inflammation[2].

The search for asthma phenotypes is an attempt to identify specific patient groups with homogeneous functional and inflammatory characteristics that may relate to clinical manifestations, prognosis, and/or response to treatment[2].

The eosinophilic asthma phenotype accounts for the majority of patients, and airway eosinophilia is indeed a marker of (i) severity of asthma, (ii) lack of asthma control, and (iii) responsiveness to steroids[2,3]. However, the importance of identifying eosinophilia in clinical practice is hampered by the lack of a simple, reliable and reproducible method of measuring it.

Eosinophilic inflammation in asthma has been assessed with invasive procedures such as biopsies and bronchoalveolar lavage[4], and with noninvasive methods such as peripheral blood cell count or biomarkers (eg eosinophil cationic protein, osteocalcin), induced sputum, and fractional exhaled nitric oxide (FeNO)[5-7]. While bronchial biopsy specimens represent the "gold standard" in terms of the target organ, induced sputum has emerged as the best proxy for clinical studies. This is both because it is the closest to bronchial biopsy specimens and/or lavage[4,7], and because it is noninvasive and relatively easy to standardize for use in clinical practice[8]. Still, significant concerns remain about the feasibility of measuring induced sputum in regular laboratories and, more important, about its reproducibility[8].

The paper by Korevaar et al. in this issue of the Journal addresses the important questions of sensitivity, specificity and predictive value of various surrogate markers for airway eosinophilia, assuming sputum eosinophilia to be the gold standard[9]. The investigators performed a meticulous systematic review and a meta-analysis that included 24 studies in adults and 8 in children. They analyzed FeNO, blood eosinophils, and serum total IgE—all of which have moderate diagnostic accuracy—as minimally invasive markers of airway eosinophilia. Most of the studies used induced sputum as a reference . The authors indicate that FeNO, blood eosinophils and IgE, if considered alone, have lower sensitivity and specificity than does induced sputum in identifying eosinophilic airway inflammation. Based on these results, Korevaar et al. state that no single surrogate marker should be used to guide treatment. Measurement of blood eosinophils would undoubtedly be the simplest way to evaluate

eosinophilic inflammation, but Schleich et al. recently described asthmatic patients with significant dissociation between blood and airway eosinophilia[5]. Korevaar et al., therefore, conclude that measuring sputum eosinophils is still the best method of identifying eosinophilic airway inflammation.

Considering the limits of these methods, one might ask once again whether practicing clinicians should measure airway eosinophilia in asthmatics. Various studies have clearly shown that therapy based on a count of sputum eosinophils is statistically more effective in controlling asthma than are clinical or functional measurements[6]. However, these studies were conducted in single specialized centres and in small groups of subjects. A larger intervention study conducted in unselected asthmatic subjects confirmed that sputum eosinophils can be used to assess the anti-inflammatory effect of treatment[10], but the variability in their results (as clearly illustrated in panel C of Figure 1) makes this method not applicable to individuals. In contrast, studies conducted in highly selected severe asthmatics with steroid-resistant sputum and circulating eosinophils have clearly shown that specific anti-eosinophilic treatment (anti-IL5, anti-IL5R, anti-IL4, anti-IL13) is highly effective both in reversing eosinophilia and in reducing exacerbations[11]. However, it is still unclear whether, even in these highly selected steroid-resistant asthmatics, eosinophils need to be measured in sputum; it appears that it might be sufficient to measure them in peripheral blood. Considering that new biological agents will soon become available for treatment of steroid-resistant eosinophilic asthmatics at risk of exacerbations[11], these patients will probably be the only ones in whom the assessment of eosinophilia will become mandatory. In this difficult population, it is possible that the use of these biological agents will be restricted to highly specialized centres where sputum eosinophilia can be reliably performed.

In conclusion, Korevaar's study points out significant differences in the accuracy of surrogate markers of airway inflammation. It also confirms that induced sputum is still the best non-invasive technique for evaluating new markers of eosinophilic airway inflammation because of its sensitivity and specificity. However, the variability between subjects reduces the usefulness of this method in clinical practice and confines it to selected patients followed in specialized centres. Measuring single surrogate markers of airway eosinophilic inflammation may therefore be an easy way to assess eosinophilic airway inflammation, but it is not necessarily the best one, and it is certainly not yet ready for use in clinical practice.

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Figure 1. Line plot of differential eosinophil counts in sputum. Showing individual profiles and time trends in two groups of asthmatic patients, one treated with inhaled high fixed dose budesonide/ formoteriol and the other with inhaled budesonide/formoterol mantainance and reliever therapy Individual profiles show large variability of % eosinophils in sputum. Modified from reference 10.