What can we learn from blood granulocyte patterns in patients with asthma?

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Blood eosinophil counts are a potentially informative biomarker in airway disease
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There has been an explosion in interest in the utility of the blood eosinophil count as a biomarker in patients with airway disease. It is a readily accessible measure, and studies have shown a consistent positive relationship between the blood eosinophil count and the risk of exacerbations [1–6], and the extent to which this can be reduced by inhaled corticosteroids (ICS) [3–5] and anti-interleukin-5 monoclonal antibodies [6–8]. Much of the work to date has been carried out in patients with severe asthma or has involved *post hoc* analysis of intervention studies of ICS in patients with moderate-to-severe chronic obstructive pulmonary disease (COPD). Much less is known about the relationship between blood eosinophil counts and outcomes in patients with less severe asthma, and there is almost no information available from longitudinal studies. The study by Nadif *et al.* [9] published in this issue of the *European Respiratory Journal* is therefore welcome, as it provides new and interesting information in both areas.

The results presented form part of the Epidemiological Study on the Genetics and Environment of Asthma (EGEA), and include a cross-sectional analysis of 232 patients with asthma and 242 symptomatic first-degree relatives of these patients. Longitudinal data over 12 years were available from 242 participants who were aged >16 years at the time of the first survey. Blood eosinophil levels were categorised as high if $\geqslant$250 cells per mm^3 and blood neutrophils if $\geqslant$5000 cells per mm^3. These pre-defined levels were based on previous data and represent the 75th percentile of the distribution of blood granulocyte counts. Relationships between blood granulocyte categories, asthma symptoms and asthma exacerbations were analysed. The authors assessed how robust these relationships were by assessing different cut-points, and by determining the relationship between asthma outcomes and consistency of inflammatory pattern. By and large, these additional analyses supported and strengthened their major conclusions.

Asthma was identified using a self-reported set of four recognised questions and/or medical record review but no up-to-date spirometry was performed. Symptom control was assessed using responses to recognised questions related to the Global initiative for Asthma definition [10]. The authors report "uncontrolled disease" in 10% and 13% of participants in the cross-sectional analysis and longitudinal analysis groups, respectively, and "partly controlled disease" in approximately a third of participants. The overall use of ICS was low in relation to the reported level of asthma control, with only 25.7% participants reporting regular ICS use within the past 12 months, a median daily dose of 250 µg (range 50–500 µg) per day and 60.3% of all participants taking no medication in the preceding 12 months. The population studied could therefore be characterised as mild by treatment requirement criteria although they were symptomatic and undertreated.

Four main blood inflammatory cell patterns were identified: paucigranulocytic (48.9%), eosinophilic (31.6%), neutrophilic (10.6%) and mixed (8.9%). These inflammatory groups were relatively stable over 12 years. How these patterns relate to airway inflammation is unclear as no direct airway measurements were made. On the basis of other studies [11, 12], it is reasonable to conclude that the eosinophilic group

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is more likely to have eosinophilic airway inflammation but no such assumptions can be made in the neutrophilic group. Systemic factors such as obesity, recent infection, age and systemic inflammation, as well more airway-specific factors such as smoking and corticosteroid use, could have influenced this measure. The neutrophil-high population tended to be older, was more female predominant and more likely to be treated with ICS, contained a higher proportion of committed smokers, and was more likely to have reported a respiratory infection within the last 4 weeks, supporting a diverse range of causes for raised blood neutrophils. In the longitudinal analysis, this population had poor asthma control and a higher frequency of exacerbations even when the analysis was adjusted for chronic bronchitis, ICS use, eosinophil counts and smoking status. Persistent neutrophilia was particularly strongly associated with these outcomes. No associations were seen with decline in lung function, a finding that is at variance with the consistent demonstration of a cross-sectional [13] and longitudinal [14] relationship between sputum neutrophil counts and decline in lung function.

In contrast, in the eosinophilic group, no obvious relationship was seen with symptoms or exacerbations, and there was no meaningful change in these variables in patients who transitioned from high to low or low to high over time. Patients in this group did have greater airway hyperresponsiveness, a lower forced expiratory volume in 1 s at follow-up and higher serum IgE. These findings differ from those of the DREAM study [6], which showed a strong positive relationship between exacerbation frequency and blood eosinophil count in patients with severe eosinophilic asthma. In addition, two large, community-based, observational studies have shown compelling evidence of a "dose–response" relationship between the blood eosinophil count and the occurrence of asthma attacks [1, 2]. One potential explanation is that ICS use obscured the relationship between exacerbation frequency and blood eosinophils in the EGEA population. It will be difficult to be sure as little can be deduced about the relationship between biomarkers and specific treatment responses in a noninterventional study such as this. A better perspective would be available from placebo-controlled trials and future studies should prospectively investigate outcomes by different blood eosinophil thresholds. *Post hoc* analysis of studies of key placebo-controlled trials might also be possible. Such analyses have been performed with several studies of ICS in patients with COPD [3–5] but not yet in patients with asthma.

The analysis by Nadif *et al.* [9] is important as it suggests that mechanisms driving symptom expression can be disassociated from more traditional asthma-related measures. It follows that therapeutic strategies might need to move on from "one size fits all" symptom-based strategies to a new approach based on analysis of the main drivers of morbidity and targeted, personalised management [15]. A key unanswered question is the extent to which blood granulocyte patterns identify "treatable traits". Although no relationship was seen between blood eosinophils and important longer-term outcomes, we believe that this measure remains the best prospect for an informative biomarker, particularly if supplemented with a more airway-specific measure such as exhaled nitric oxide. There is also the tantalising prospect that these measures can be used to identify the main drivers of type-2 high inflammation and individualise treatment approaches [16].

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