



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

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

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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 exacerbations¹⁻⁶, and the extent to which this can be reduced by inhaled corticosteroids³⁻⁵ and anti-IL-5 monoclonal antibodies⁶⁻⁸. 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 inhaled corticosteroids in patients with moderate to severe 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 al⁹ published in this issue of the 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) group and included a cross sectional analysis of 232 patients with asthma and 242 symptomatic first degree relatives of these patients. Longitudinal data over 12 years was available from 242 participants who were aged >16 years at the time of the first survey. Blood eosinophil levels were categorised as high if ≥ 250 cells/mm³, and blood neutrophils if ≥ 5000 cells/mm³. These pre-defined levels were based on previous data, and represented the 75th percentile of the distribution for 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 definition¹⁰. The

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3 authors report 'uncontrolled disease' in 10% and 13% of participants in the cross-sectional analysis
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5 and longitudinal analysis groups respectively and 'partly controlled disease' in approximately a third
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7 of participants. The overall use of inhaled corticosteroids (ICS) was low in relation to the reported
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9 level of asthma control, with only 25.7% participants reporting regular ICS use within the past 12
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11 months and a median daily dose was 250µg/day (range 50-500) and 60.3% of all participants taking
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13 no medication in the preceding 12 months. The population studied could therefore be characterised
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15 as mild by treatment requirement criteria although they were symptomatic and undertreated.
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20 Four main blood inflammatory cell patterns were identified: paucigranulocytic (48.9%), eosinophilic
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22 (31.6%), neutrophilic (10.6%) and mixed (8.9%). These inflammatory groups were relatively stable
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24 over 12 years. How these patterns relate to airway inflammation is unclear as no direct airway
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26 measurements were made. On the basis of other studies^{11,12}, it is reasonable to conclude that the
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28 eosinophilic group are more likely to have eosinophilic airway inflammation but no such
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30 assumptions can be made in the neutrophilic group. Systemic factors such as obesity, recent
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32 infection, age and systemic inflammation as well more airway specific factors such as smoking and
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34 corticosteroid use could have influenced this measure. The neutrophil high population tended to be
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36 older, more female predominant, more likely to be treated with inhaled corticosteroids, contained a
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38 higher proportion of committed smokers, and were more likely to have reported a respiratory
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40 infection within the last 4 weeks, supporting a diverse range of causes for raised blood neutrophils.
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42 In the longitudinal analysis, this population had poor asthma control and a higher frequency of
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44 exacerbations even when the analysis was adjusted for chronic bronchitis, ICS use, eosinophil counts
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46 and smoking status. Persistent neutrophilia was particularly strongly associated with these
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48 outcomes. No associations were seen with decline in lung function, a finding that is at variance with
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50 the consistent demonstration of a cross-sectional¹³ and longitudinal¹⁴ relationship between sputum
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52 neutrophil counts and decline in lung function.
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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 FEV1 at follow-up and a higher serum IgE. These findings differ from those of the DREAM study⁶, which showed a strong positive relationship between exacerbation frequency and blood eosinophil count 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 inhaled corticosteroid 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 non-interventional 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 done with several studies of inhaled corticosteroids in patients with COPD³⁻⁵ but not yet in patients with asthma.

The analysis of Nadif et al 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 management¹⁵. 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 (FeNO). 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 approaches¹⁶.

References

1. Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *The Lancet Respiratory medicine* 2015; **3**(11): 849-58.

2. Malinovschi A, Fonseca JA, Jacinto T, Alving K, Janson C. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. *J Allergy Clin Immunol* 2013; **132**(4): 821-7.e1-5.

3. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. *The Lancet Respiratory medicine* 2015; **3**(6): 435-42.

4. Pavord ID, Lettis S, Locantore N, et al. Blood eosinophils and inhaled corticosteroid/long-acting beta-2 agonist efficacy in COPD. *Thorax* 2016; **71**(2): 118-25.

5. Siddiqui SH, Guasconi A, Vestbo J, et al. Blood Eosinophils: A Biomarker of Response to Extrafine Beclomethasone/Formoterol in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med* 2015; **192**(4): 523-5.

6. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012; **380**(9842): 651-9.

7. Castro M, Wenzel SE, Bleecker ER, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *The Lancet Respiratory medicine* 2014; **2**(11): 879-90.

8. Castro M, Zangrilli J, Wechsler ME, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *The Lancet Respiratory medicine* 2015; **3**(5): 355-66.

9. Nadif R, Siroux V, Boudier A, et al. Blood granulocyte patterns as predictors of asthma phenotypes in adults from the EGEA study. *Eur Respir J* 2016 in press.

10. Reddel HK, Bateman ED, Becker A, et al. A summary of the new GINA strategy: a roadmap to asthma control. *European Respiratory Journal* 2015.

11. Schleich F, Corhay JL, Louis R. Blood eosinophil count to predict bronchial eosinophilic inflammation in COPD. *Eur Respir J* 2016; **47**(5): 1562-4.

12. Wagener AH, de Nijs SB, Lutter R, et al. External validation of blood eosinophils, FE(NO) and serum periostin as surrogates for sputum eosinophils in asthma. *Thorax* 2015; **70**(2): 115-20.

13. Shaw DE, Berry MA, Hargadon B, et al. Association between neutrophilic airway inflammation and airflow limitation in adults with asthma. *Chest* 2007; **132**(6): 1871-5.

14. Stanescu D, Sanna A, Veriter C, et al. Airways obstruction, chronic expectoration, and rapid decline of FEV1 in smokers are associated with increased levels of sputum neutrophils. *Thorax* 1996; **51**(3): 267-71.

15. Agusti A, Bel E, Thomas M, et al. Treatable traits: toward precision medicine of chronic airway diseases. *Eur Respir J* 2016; **47**(2): 410-9.

16. Pavord ID, Hilvering B. Biomarkers and inhaled corticosteroid responsiveness in asthmatic patients. *J Allergy Clin Immunol* 2015; **135**(4): 884-5.