

EDITORIAL

Clinical & Experimental Allergy

More (on) airway eosinophilia in asthma

This editorial discusses the findings of the article in this issue by S. Cianchetti et al. [12] pp. 673–680.

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Under the umbrella of the term ‘asthma’, there are conditions heterogeneous with respect to clinical features, functional impairment, type of airway inflammation and response to drug treatment. Clinicians have long recognized different phenotypes of asthma. The characterization of intrinsic (later onset, non-allergic) and extrinsic (earlier onset, allergic) asthma was developed several decades ago [1]. This distinction is not used any more in the current international guidelines, after some studies showed that airway pathology, IgE and Th2-cytokine levels, and response to corticosteroid treatment was similar in the two variants of the disease [2].

More recently, the investigation of asthma phenotypes has evolved with the use of multi-variate unbiased approach. A number of cluster analyses have identified several asthma phenotypes. Most investigation ended up with 4–7 distinct phenotypes [3–6]. Considering the diversity in the populations examined (European, Korean and North American) and in the methodology among the above investigations, there are more similarities than differences in the results. For instance, the two studies with extensive number of variables applied to relatively small populations both identified five clusters [3, 4]. Some of them were remarkably similar, such as the cluster of asthma in obese non-atopic females. In addition, adult asthma phenotypes identified by a clustering approach were highly consistent 10 years apart [5]. The key benefit of dividing a multi-dimensional disease into distinct phe-

notypes is expected to be more effective treatment targeting. Cluster analysis has indeed contributed to identify the elements that make asthma heterogeneous, but the usefulness of this approach for the management of the patients has not been demonstrated yet.

The attempt to assign asthmatics to distinct phenotypes by simpler univariate separation based on predetermined parameters (degree of obstruction on spirometry or frequency of symptoms) was the approach used by international guidelines for asthma classification and treatment [2]. The application of GINA and national guidelines provided an improvement of asthma education and care using conventional anti-asthma drugs, such as bronchodilators and corticosteroids.

The introduction of new expensive biological agents for treating severe asthma has enhanced the interest in characterization of those individuals who will have the most benefit from or have the highest probability to respond positively to a specific treatment. The first biological agent approved for asthma, anti-IgE monoclonal antibody (omalizumab), is indicated and effective for the phenotype of severe asthma characterized by perennial allergy and increase in total serum IgE [7]. Monoclonal antibodies to IL-5 failed to show clinical benefit in non-phenotyped asthma, whereas they were effective in reducing exacerbations in subgroups of severe asthmatic with eosinophilia refractory to corticosteroid therapy [8, 9]. Treatment with a monoclonal antibody to IL-13 produced the highest improvement in patients with moderate to severe corticosteroid-treated asthma exhibiting high Th2 signature assessed by serum levels of periostin [10].

Phenotyping or endotyping asthma has contributed to optimization of treatment. However, the findings from these studies leave open some questions on the role of eosinophils in asthma, as the efficacy of anti-IL-13 monoclonal antibodies was observed in the absence of a reduction in eosinophils, and the failure of anti-IL-5 antibodies occurred despite a reduction in eosinophils [11].

In this issue of *Clinical & Experimental Allergy*, Cianchetti et al. [12] provide some new information on

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eosinophilic inflammation in asthma. They performed a retrospective study in 186 consecutive patients, steroid-naïve, with mild to moderate asthma, evaluated for the first time in the asthma clinic of their university hospital. The aim was to assess whether sputum eosinophils and sputum eosinophil cationic protein (ECP) were differently related to several clinical and functional parameters. The patients were divided into four groups on the basis of sputum eosinophils percentage ($> 2\%$ or $\leq 2\%$) and sputum ECP values ($> 75 \mu\text{g/mL}$ or $\leq 75 \mu\text{g/mL}$). The results confirm that the pattern of airway inflammation is heterogeneous in asthma. Overall, both increased sputum eosinophils and increased ECP levels were related to increasing severity of clinical presentation assessed by asthma symptom score and use of short-acting bronchodilators.

An interesting finding is a poor concordance between the two indexes of airway eosinophilia, percentage of eosinophils and ECP levels, with discordant results in 38.8% of the cases. This implicates that individuals without increased percentages of sputum eosinophils may actually have evidence of eosinophilic airway inflammation based on increased ECP. Considering both markers, the proportion of mild/moderate asthmatics without evidence of airway eosinophilia is limited to 20%. This percentage is lower than that is generally reported (approximately 50%) [11, 13] and is of interest since Cianchetti et al. [12] examined asthmatic subjects free from corticosteroid therapy. In studies of asthmatic subjects treated with corticosteroids, it is not possible to determine whether a lack of sputum eosinophilia is a consequence of corticosteroid therapy or represents a true non-eosinophilic phenotype. Indeed, longitudinal sputum assessment and corticosteroid withdrawal studies have shown that the sputum eosinophil count in asthmatic subjects treated with corticosteroid is variable and changes in response to disease stability and current therapy. A stepwise regression analysis showed weak, albeit significant, inverse correlations between eosinophil count and disease duration, and between ECP and airflow obstruction, suggesting that these biomarkers might identify different aspects of the disease. The explanation of these findings remains speculative given the observational nature of the study [12]. The reason of longer duration of the disease in those patients with lower eosinophil counts might be simply due to the mildness of the disease in non-eosinophilic subgroup, resulting in delay in seeking medical attention and/or in the first

access to an asthma specialist. More intriguing is why sputum ECP was more closely related to lung function than eosinophil counts. The literature is controversial regarding this issue, and the work by Cianchetti et al. [12] contributes with a number of subjects higher than that in previous studies, but not with a clarification.

It is well established that the asthmatics who most benefit of corticosteroid therapy are those with eosinophilic airway inflammation, and management guided to achieve control of eosinophilic airway inflammation results in a reduction in the risk of asthma exacerbations [14]. The identification of eosinophilic asthma implicates the analysis of airway eosinophils. The best method to do this is the induced sputum differential leucocyte cell count. However, it is time-consuming, not always successful, and not widely adopted in clinical care settings. The results of Cianchetti et al. [12] could help to restrict the indication to airway eosinophilia assessment. Their findings implicate that eosinophilic asthma, in steroid-naïve patients, is expected to be present in most cases of mild to moderate disease (80%). Therefore, there is indication to initiate inhaled corticosteroid treatment. The remaining 20% non-eosinophilic asthmatics include subjects with low daily symptom score, little use of bronchodilators and normal lung function, that is, patients with benign disease who will need symptomatic treatment only to be controlled. Therefore, the first treatment for mild to moderate asthma could reasonably be assigned without airway inflammation assessment. Unfortunately, we are not in the position to generalize the findings of Cianchetti et al. [12], as their patients were recruited by a single centre introducing a risk of selection bias, the number examined was relatively small, and 30% patients were not able to produce adequate sputum sample, preventing the assessment of airway inflammation. We know that the response to corticosteroids in asthma is heterogeneous. There are cases of eosinophilia resistant to treatment and cases that, despite the suppression of eosinophils by corticosteroids, remain with unsatisfactory control of their asthma. Indication to airway inflammation assessment could be limited to those subjects who do not respond as expected to corticosteroid treatment and to severe asthma, where inflammatory phenotyping is necessary to target the most appropriate treatment.

Conflict of interest: The author declares no conflict of interest.

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