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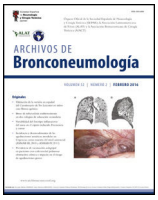

Editorial

Might basophils be a reliable biomarker in severe asthma?☆

En busca de un biomarcador fidedigno en el asma grave: ¿el basófilo?

The emergence of biological drugs for the treatment of severe asthma has meant a dramatic change in the quality of life of patients, and has contributed to a significant decrease in exacerbations. Although there is still a group of asthma patients whose pathogenesis is less clear, about 50% represent an inflammatory endotype (T2 inflammatory response) which is the therapeutic target of biological drugs currently in use. While the response to anti-interleukin 5 drugs (mepolizumab, reslizumab, and benralizumab) can be expected to be better when the clinical phenotype is clearly eosinophilic, the clinical response to omalizumab is much more variable and difficult to predict, as it has been shown to be effective in patients with non-allergic asthma, probably due to the large overlap between the immunopathological mechanisms of the disease[1].

At present, the integration of the different "omics" applied to sputum, blood and exhaled air is in the early stages of research, so we still have few clinically useful biomarkers[2]. As such, the most commonly used T2 markers include FeNO, total and specific IgE, and eosinophilia in blood and sputum. However, even in combination, these markers have shown little phenotype specificity or endotype sensitivity, although they are used, paradoxically, to classify patients by phenotypes and guide treatment[3].

Basophils play an important role in the development of airway inflammation as originators of inflammatory mediators central to the pathogenesis of allergic disease[4] (such as preformed histamine and C4 leukotriene). These mediators are released minutes after binding with the high-affinity IgE receptor, FcεRI, or later by an IgE-independent mechanism[5].

Basophils not only constitute one of the most important groups of effector cells, but are also involved in the release of various interleukins (IL), primarily IL-4 and IL-13. In fact, several studies have shown that by producing IL-4, basophils facilitate the Th2 activities of other immune cells, including T cells, B cells, monocytes, type 2 innate lymphoid cells[6], and eosinophils. Moreover, eosinophilic tissue infiltration, mediated by IL-4, is attributed to basophils[7].

Basal expression of the IL-25 and IL-33 receptors on the basophil membrane has also been reported to be significantly higher in patients with severe vs. mild asthma, regardless of the degree of asthma control, the existence of atopy, the number of exacerbations, or the degree of eosinophilia. Basophils have also been detected in significantly higher numbers in bronchial biopsies[8], in induced sputum, and in bronchoalveolar lavage in patients with severe asthma[9,10].

Finally, not only is the proportion of basophils in the blood of asthma patients significantly higher than in healthy subjects, but some studies have also shown a marked reduction in the surface expression of the IL-18 receptor involved in the pathogenesis of asthma[11].

As regards clinical research, studies carried out in patients with urticaria have shown that the best responses to omalizumab occur in patients who have a higher concentration of FcεRI in basophils, and clear cut-off points could even be established[12]. Could the same be true of asthma patients? There are few studies in this regard, and further research is needed. Pereira Santos et al. published a study[13] of only 2 patients with allergic asthma treated with omalizumab. The authors observed a marked reduction in surface IgE and FcεRI on basophils, and a reduction in basophil activation after allergen stimulation. These effects were already evident after one month, but increased after 3, 6, and 12 months of omalizumab treatment, raising the hypothesis that it might be a useful marker for evaluating response to the drug. Along the same lines, a second study carried out in 32 patients evaluated the effect of omalizumab treatment according to the allergen sensitivity threshold, also called CD-sens[14]. Treatment with omalizumab reduced basophil response to allergen stimulation measured by CD-sens, indicating a successful inhibition of basophil activation and IgE-mediated inflammation. The authors thus proposed using CD-sens to adjust the dose of omalizumab required by each patient.

At the latest SEPAR conference, our group presented the preliminary results of a study in which we tried to correlate basophil sensitivity in asthma patients, measured by the basophil activation test (BAT or basotest), with clinical parameters and response to treatment with omalizumab[15]. BAT is a technique that has been used for years, and when combined with flow cytometry it can be used in clinical practice to study drug and food allergies, to follow-up the efficacy of immunotherapy, in desensitization procedures, and to study allergic processes in which specific IgE cannot be detected by conventional methods. Our results indicate that, compared with non-omalizumab responders, basophils in asthma patients in whom omalizumab treatment is effective respond to significantly higher stimulus concentrations via FcεRI. This would imply that response to omalizumab treatment is associated with a substantial decrease in basophil sensitivity through the high-affinity IgE receptor.

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Determining the clinical impact of loss of basophil sensitivity could be useful for endotyping patients, and could be used as a predictor of response to omalizumab or future therapies targeting the IL-5 axis, which has powerful effects on eosinophils and basophils. It appears to be an ambitious goal and much remains to be learned, but if positive results are achieved, they would be highly applicable in everyday clinical practice.

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