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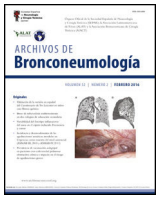

Editorial

Current Role of Biomarkers in Severe Uncontrolled Asthma☆

Papel de los biomarcadores en el asma grave no controlada en la actualidad

Ebymar Arismendi,[a,b,*] César Picado Vallés[a,b,c]

[a] Servicio de Neumología, Hospital Clínic de Barcelona, Barcelona, Spain
[b] CIBER Enfermedades Respiratorias (CibeRes), Madrid, Spain
[c] IDIBAPS-Universitat de Barcelona, Barcelona, Spain

The determination of various biomarkers in patients with severe uncontrolled asthma is currently considered indispensable. This information helps determine the bronchial inflammatory profile, define the asthma phenotype, and guide the possible therapeutic options.[1–3] Over the past 2 decades, significant advances in immunology and molecular biology have led to the development of biological therapy targeted at some of these biomarkers in the treatment of severe uncontrolled asthma. A recent monograph on severe asthma published by the European Respiratory Society[4] reviewed the definitions accepted by the Biomarker Working Group of the Food and Drug Administration and the National Health Institute.[5] These guidelines describe a biomarker as a measurable characteristic that is an indicator of normal biological processes, pathogenic processes, or responses to exposure or intervention, including therapeutic interventions. The authors propose 7 possible categories for biomarkers: diagnosis, monitoring, response, prognosis, susceptibility/risk, safety, and prediction.[5]

The history of biomarkers in asthma is relatively recent, dating back 20 years to when Wenzel et al.[6] observed in 1999 that patients with higher blood eosinophil counts had more severe asthma than those with lower concentrations. These eosinophilic patients also showed greater basal membrane thicknesses in bronchial biopsies, suggesting that they had undergone an intense process of airway remodeling. About 10 years later, Woodruff et al.[7] reported that a group of asthma patients presented a very intense inflammatory process characterized by increased eosinophils in blood and in bronchoalveolar lavage, raised periostin levels, and a thicker basal membrane in bronchial biopsies, all associated with a more intense response to inhaled corticosteroids. This group of patients was defined as Th2-high phenotype, based on the belief that such inflammation was basically mediated by type 2 helper T cells. This Th2-high phenotype is defined mainly by the presence of eosinophils in blood and sputum, high levels of fractional exhaled nitric oxide, and raised serum levels of periostin and immunoglobulin E (IgE). Th2-high patients express higher levels of interleukin (IL)4, IL5 and IL13 in bronchial biopsies, and show higher bronchial hyperreactivity and higher mucin gene expression in the airways. In other words, this Th2-high phenotype encompasses several of the phenotypes described in the literature, such as severe allergic asthma and non-allergic eosinophilic asthma. This inflammation has recently been renamed T2 inflammation, since other immune cells involved as mediators such as type 2 innate lymphoid cells have been observed.[8] Patients who did not express this marked inflammation were practically indistinguishable from healthy subjects and were assigned the Th2-low phenotype.[7]

Several biomarkers have been described in the T2-high severe uncontrolled asthma phenotype, and while the list is extensive, biomarkers that currently have an impact on clinical practice are IgE, eosinophils in blood and/or sputum, and fractional exhaled nitric oxide, although the diagnostic/therapeutic role of the latter remains controversial in the clinical practice guidelines.[1,2] Firstly, IgE is one of the most widely used biomarkers in allergic asthma. IgE blockade with omalizumab produced excellent results after more than 10 years of use as additional treatment in patients with allergic severe uncontrolled asthma in a real world setting.[9] The importance of IgE beyond allergic asthma has been established in a series of studies, one of the findings of which was that IgE binding to high affinity receptors can induce intracellular signaling responsible for the production of cytokines (IL4, IL6, IL13, etc.) and stimulate mast cell activation without the need to bind with allergens.

Eosinophils, for their part, have become one of the most studied cells in asthma in recent years.[10] This research has had a great impact on modern biological treatment, since the T2-high eosinophilic phenotype involves the increased expression of certain cytokines, such as IL4, IL33 and IL5, which are among the main therapeutic targets at present. Today 3 different biological treatments that act on IL5 are available: mepolizumab[11] and reslizumab,[12] which act by directly blocking IL5, and benralizumab,[13] which acts on the IL5 receptor α. These biologics have recently been approved for the treatment of severe eosinophilic asthma, after they were seen to be highly effective in pivotal studies. Other biologics are also available for the treatment of severe uncontrolled asthma, some of which are still in the experimental phase, such as dupilumab,[14] which blocks the IL4/IL13

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* Corresponding author.
E-mail address: earismen@clinic.cat (E. Arismendi).

receptor and will shortly be marketed in Spain. With respect to the T2-low phenotype, neutrophils in sputum and some interleukins such as IL17 and IL8 have been proposed as biomarkers, but so far none have been associated with any targeted biological treatment and their usefulness in clinical practice is limited.

Numerous biomarkers are being evaluated with the aim of selecting the most suitable treatment for each patient with severe uncontrolled asthma. These include volatile organic compounds, the determination of pH in exhaled breath condensate, IL6 and other cytokines, using proteomics, metabolomics and transcriptomics which could help determine the various inflammatory pathways that may be involved.[15,16] One of the most important endeavors at the moment is to define clinically useful/therapeutic biomarkers in patients with non-T2 or T2-low phenotype, as the mechanisms underlying this inflammation remain unclear and poorly understood, and no biologic targeted at this patient phenotype is currently available. Biomarkers play an essential role in asthma today, and must be determined in all patients with uncontrolled severe asthma correct diagnostic and therapeutic decision-making. Furthermore, new biomarkers are needed to help not only decide between different therapeutic options, but also to predict response to these treatments, so all possible mechanisms involved in inflammation and the pathophysiology of uncontrolled severe asthma should be further investigated, especially in the T2-low phenotype.

Conflict of Interests

Ebymar Arismendi has received honoraria as a speaker, scientific advisor, and clinical trial investigator from (in alphabetical order): AstraZeneca, Bial, Chiesi, GlaxoSmithKline, Novartis and Teva.

César Picado Vallés has received honoraria as a speaker, scientific advisor, and clinical trial investigator from Novartis.

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