Biomarkers of Allergic Asthma

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Allergic asthma is the most common asthma phenotype and is characterized by IgE sensitization to airborne allergens and subsequent typical asthmatic symptoms after exposure. A form of type 2 (T2) airway inflammation underlies allergic asthma. It usually arises in childhood and is accompanied by multimorbidity presenting with the occurrence of other atopic diseases, such as atopic dermatitis and allergic rhinitis. Biomarkers identifying patients with allergic asthma include total immunoglobulin E (IgE) levels, fractional exhaled nitric oxide (FeNO) and serum eosinophil counts.

Keywords: allergic asthma ; asthma ; allergic phenotype ; biomarkers

1. Introduction and Definition

Asthma is a chronic heterogeneous disease affecting more than 330 million people worldwide [1][2]. It constitutes a significant socioeconomic burden, especially in its severe uncontrolled form [3]. Over the next 20 years, asthma management in the United States is predicted to cost more than $960 billion [4]. Asthma is usually characterized by chronic airway inflammation and variable symptoms including cough, chest tightness, shortness of breath and wheezing, along with variable expiratory airflow limitation, which can become persistent due to airway remodeling [5]. Based on age of onset, atopy status, preservation of airflow, comorbidities, exacerbations, response to treatment and prognosis, as well as the underlying airway inflammation, different phenotypes and endotypes are embraced by the definition of asthma [6]. Hence, “asthma” has been proposed as an umbrella term under which all these phenotypes and endotypes, frequently overlapping, lie, with allergic asthma holding a key position [7]. It is estimated that allergic mechanisms are present in about 80% of child asthmatics and 40–50% of adult asthmatics [8]. Thus, the allergic phenotype is the most common asthma phenotype in the general asthma population [9][10] and the most commonly reviewed allergic disease in the literature [11]. The frequency of allergic asthma and the difficulty in precisely recognizing and differentiating it from other type 2 (T2) overlapping endotypes in clinical practice constitute a great challenge in the era of the pursuit of therapeutic strategies made to measure for every patient; that is, the era of precision medicine and tailor-made interventions.

Since the nature of asthma is complex and heterogeneous, framing the definition of allergic asthma is a great challenge. An “allergy”—and, therefore, “allergic”—is currently defined as an immune-mediated hypersensitivity reaction [8]. Recently, however, a more provocative—albeit refreshing—definition has been proposed [12]. Allergic asthma is usually defined as asthma associated with sensitization to aeroallergens. This definition consists of two criteria: (A) identification of allergic sensitization (in vivo and/or in vitro) and (B) association between aeroallergen exposure and asthma symptoms [9]. However, allergic asthma is often defined in the literature only with regard to the presence of sensitizations independently of their correlation with symptoms, thus further blurring the picture of this phenotype. Moreover, severe asthma represents one of the main goals of precision medicine, with monoclonal antibodies being at the forefront. Hence, when choosing a biologic agent, a stricter definition of allergic asthma is required. As derived from the populations of the randomized controlled trials (RCTs) that informed the regulatory approval in current published guidelines regarding biologics for severe asthma, the allergic subtype is clearly distinguished from the eosinophilic one. It is defined as the asthma phenotype characterized by symptoms resulting from exposure to a perennial aeroallergen and serum total IgE levels of 30–1300 IU/mL that are not adequately controlled with high doses of inhaled corticosteroids/long-acting beta2-agonists (ICSs/LABAs) and/or other background controllers [13]. This definition seems to be of particular use in the selection of omalizumab-eligible patients within the context of personalized medicine for severe allergic asthma. However, to complicate the puzzle even more, despite the clear distinction between allergic and eosinophilic asthma stated in current guidelines, different treatment options are currently proposed that ignore or misconceive the overlapping natures of these subtypes in clinical practice [13][14].

2. Biomarkers of Allergic Asthma

A biomarker can be defined as any objectively measured characteristic that can be used as an indicator of disease diagnosis, a predictor of response to treatment and for monitoring [15]. To be applicable in clinical practice, a biomarker should be able to define a phenotype and/or an endotype, predict and evaluate treatment response and monitor disease progression [16]. As we enter the era of personalized medicine, identifying the perfect biomarker with the abovementioned characteristics is urgently needed, especially in allergic and other T2-overlapping severe asthma endotypes, for which the choice of the ideal treatment for each patient is quite challenging [17]. Although several biomarkers have been proposed to be associated with T2 inflammation, allergic asthma often presents with elevated levels of immunoglobulin E (IgE), FeNO, blood and sputum eosinophils and periostin [17].

2.1. Total and Specific Immunoglobulin E (IgE)

Measurement of total IgE levels and sensitization rates to environmental allergens, either through measurement of specific IgEs in serum and/or by in vivo performance of skin tests, have been used to identify patients with allergic asthma. A relationship between total IgE levels and allergic asthma has been shown [18]. Although no association with asthma severity was shown, IgE levels were associated with hospitalization rates and use of inhaled corticosteroids (ICS) in the Epidemiological Study on the Genetics and Environment of Asthma (EGEA) study [18]. In another study by Fitzpatrick et al., IgE levels were positively correlated with asthma severity [19]. Although the inextricable link between atopy and asthma is beyond question, it is well-accepted that not all atopics will show a clinical presentation of their IgE sensitization and, thus, development of allergic asthma [20]. Hence, it is important to highlight that allergen sensitization alone does not necessarily mean a clinically relevant allergy and expression of allergic asthma. Measurements of specific IgEs and skin prick tests for whole allergen extracts cannot differentiate between asymptomatic and clinically relevant sensitization. However, component-resolved diagnosis has emerged as a possible diagnostic tool in asthma and as a way to measure biomarkers for symptomatic sensitization [21]. Identification of sensitization clusters based on measurements and interactions of allergen components have shown that interplay between pairs of specific allergen components is associated with increased risk of asthma [22]. Moreover, in mite-sensitized children, the immunoglobulin G/immunoglobulin E ratio was significantly lower in children with asthma compared to those without asthma [23].

2.2. Fractional Exhaled Nitric Oxide (FeNO)

FeNO is a non-invasive biomarker associated with eosinophilic airway inflammation that can easily be measured in preschoolers [24][25][26]. IL-13 stimulates nitric oxide synthase in bronchial epithelial cells and leads to a subsequent increase in FeNO levels [27]. A modest association between eosinophilic airway inflammation and FeNO levels has been previously shown [28]. The Global Initiative for Asthma (GINA) recommends FeNO levels above 25 parts per billion (ppb) as a marker of T2 inflammation when assessing severe asthmatic patients [14].

FeNO levels above 50 ppb and 35 ppb in adults and children, respectively, are associated with eosinophilic inflammation and response to ICS [29]. However, FeNO levels can be elevated in cases of allergic rhinitis, atopy, eosinophilic bronchitis and atopic dermatitis and reduced in smokers or during bronchoconstriction. Viral exposure can result either in reduced or increased levels of FeNO [25].

Results from the Severe Asthma Research Cohort indicate that elevated levels of FeNO were associated with early-onset asthma, atopy and airway hyperreactivity [24]. A recent systematic review and metanalysis showed that measurement of FeNO levels has high specificity for diagnosis of asthma, with higher cut-off values (>50 ppb) increasing specificity further [30].

2.3. Eosinophils

Sputum eosinophil is one of the most well-characterized biomarkers for the assessment of severe asthma. Due to limitations in obtaining samples, especially in pediatric populations, it is usually performed in centers specializing in severe asthma in adult populations [16]. Results from a systematic review and meta-analysis indicated that sputum eosinophilia was moderately correlated with blood eosinophils, FeNO levels and total serum IgE [28].

Although elevated levels of eosinophils usually suggest response to corticosteroid therapy, they may indicate poor adherence or incorrect technique in ICS therapy [31][32].

Due to a reduction in exacerbation rates when a sputum-guided management was followed in severe asthmatics [33], GINA and European Respiratory Society/American Thoracic Society (ERS/ATS) recommend sputum-guided therapeutic interventions for severe asthma populations in specialized centers [34][35].

Measuring blood eosinophils is an easy intervention, and blood eosinophil is widely used as an eligibility marker (different cut-offs in different countries) for anti-IL-5 monoclonal antibody selection and as a predictor of response [34]. However, use of systemic corticosteroids, age and concomitant atopic disease has to be considered when evaluating blood eosinophils [36].

In a cross-sectional study, blood eosinophils, sputum eosinophils and elevated levels of total IgE (>100 IU/mL) were significantly correlated with severe persistent asthma [37]. In a systematic review and meta-analysis, Korevaar et al. found only moderate accuracy regarding the use of blood eosinophils, IgE and FeNO in predicting airway eosinophilia. If these biomarkers are considered in isolation, they have low sensitivity and specificity in identifying airway inflammation compared to sputum eosinophils [28]. Higher levels of peripheral eosinophils and TH2-polarized responses have been identified in patients with allergic asthma compared to those with non-allergic asthma [38]. Blood eosinophil levels in patients with allergic asthma vary according to different studies, with elevated levels (>300 cells/μL) being present in about 50% of patients in RCT and real-life studies [39][40][41]. In the STELLAIR study, a retrospective real-life study assessing omalizumab effectiveness in patients with allergic asthma, blood eosinophil count was ≥300 cells·μL^{-1} in 52.1% of the adults and 73.8% of the pediatric population [39]. In another real-life yet retrospective study, blood eosinophils ranged between 0 and 2340 cells/μL in 711 patients at baseline, with 35.4% of patients having levels >300 cell/μL [40].

2.4. Serum Periostin

Periostin, a matricellular protein that is upregulated by T2 cytokines, IL-4 and IL-13 in bronchial epithelial cells, is involved in T2 inflammation and airway remodeling in asthma [42][43]. The ability to measure periostin in the serum of asthmatic patients makes it a useful biomarker in assessing T2 inflammation and remodeling [44][45]. Measurement of serum periostin correlates with other T2 biomarkers, such as IgE levels, serum eosinophils, eosinophilic cationic protein and airway hyperresponsiveness [46][47].

Finally, the potential use of periostin as a biomarker in pediatric populations is yet to be explored since, due to bone growth, baseline periostin levels are higher in children [48].

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