Biomarkers in Severe Asthma

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Abstract

Asthma is the most common chronic respiratory disease, affecting both children and adults. It is an umbrella term, encompassing multiple phenotypes. Asthma phenotypes may also be identified as clusters of measurements from different dimensions of the disease, and are partly genetically determined. The mechanisms leading to the disease are complex and it is still a challenge to choose suitable biomarkers, which have become especially important with the introduction of biological asthma treatment. Asthma can be broadly divided into T2-high and T2-low molecular endotypes. Early-onset asthma is typical of allergic phenotype and has so far been the most extensively investigated. The prevalence of adult-onset asthma i si increasing because of the ageing population. This asthma phenotype can be divided into two types considering the existence of eosinophilic inflammation. Various other asthma phenotypes, for instance, exercise-induced, and obesity or smoking-associated asthma, should be taken into account when evaluating the patient. Severe asthma,with the prevalence of 5-10% of all asthma patients, remains a clinical challenge. Various biomarkers are thus under investigation in the hope of helping researchers and clinicians in better disease evaluation since the individual approach and personalized medicine are imperative.

Keywords: asthma phenotype, clusters, biomarkers, eosinophils

Introduction

Asthma is the most frequent chronic respiratory disease[1], with almost 1 in 8 children and 1 in 12 adults affected[2]. Since 2016, the Global initiative for asthma (GINA) has stated that asthma is a heterogeneous disease[3]. Asthma phenotyping is needed for a more precise patient approach and a better understanding of asthma diversity. Asthma heterogeneity is seen in diverse clinical presentations, different responses to treatment, and different pathophysiological features and findings due to various pathogenic mechanisms, which lead to multiple asthma phenotypes.

Phenotype is by definition an observable disease characteristic which is the result of gene-environment interaction. These characteristics can be disease symptoms, triggers, body shape and weight, age of asthma onset, etiology, atopic status, response to the smoking habit, laboratory findings, biomarkers, lung function parameters and presence of chronic airflow obstruction, bronchodilator reversibility, reaction to drugs or substances, response to treatment, level of asthma control, number of exacerbations, severity and speed of asthma deterioration, need for hospitalization or intensive care unit treatment, including mechanical ventilation, duration

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of quiescent state of asthma, involvement of upper respiratory airways and/or nasal polyps etc. The topic concerning asthma phenotypes is very important as personalized, individually tailored treatment adjusted to the understanding of underlying phenotype mechanisms yields much better results in asthma patients[4,5].

Asthma phenotype description dates from the mid-20th century, with Rackeman's idea from 1947 about extrinsic and intrinsic asthma, emphasizing the triggering role of allergens in asthma[6]. After the enthusiasm for inhaled corticosteroid treatment in asthma in the'80s of the previous century, and the introduction of LABAs (long acting beta agonists) in asthma treatment in the '90s[7], with much better achievements in asthma control, the first decade of the new millennium brought a rise in the asthma heterogeneity awareness[8].

However, observable characteristics are not enough, because of many overlapping symptoms of the disease, so the common underlying pathophysiological mechanism in asthma is important. Due to these facts, a new term was developed - asthma endotypes[9].

Biomarkers are specific measurable disease characteristics. These are quantifiable factors distinguishing between physiological and pathological processes and could be used as a pathway for therapy selection and therapeutic response monitoring[10]. The mechanisms leading to the disease are complex and it is still a challenge to choose suitable biomarkers to adequately stratify patients, which became especially important with the introduction of biologicals in asthma treatment[11]. The key point is biomarkers for the endotypic (and phenotypic) criteria. The right combination of various biomarkers in different phenotypes is under investigation hoping to help researchers and clinicians in better disease evaluation since the individual approach and personalized medicine are imperative[11,12]. Today, defining a severe asthma phenotype is a process based on a biomarker-driven approach[10]. There is no perfect biomarker, and unlike for some other disorders, biomarkers for asthma are less precise, and still not completely known. Generally, based on these markers, asthma can be divided into two groups, T2-high asthma, and T2-low (or non-T2) asthma[11,10].

Continuous improvement of asthma phenotypes and their identification has led to an individualized, targeted approach in asthma therapy, especially in severe cases. Biomarkers are the key to understanding and recognizing phenotypes, and accordingly the key to therapy and treatment assessment.

Type 2 high-inflammation asthma is characterized by eosinophilic airway inflammation, while type 2 low-inflammation asthma includes neutrophilic and paucigranulocytic asthma. A larger proportion of cases of severe asthma are type 2-high asthma[17,18].

A high level of type 2 cytokines is characteristic of T2-high asthma, and those areIL-5, IL-4, IL-13, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Biomarkers of type 2 inflammation have proven valuable for endotyping in asthma[17,18].

Biomarker: Type 2 Inflammation

Blood Eosinophils

Eosinophils are specialized leukocytes produced in the bone marrow, primarily found in tissues and in the respiratory system, airway mucosa, and airways, which promote inflammation by releasing an abundance of inflammatory mediators. These mediators, together with those released from T2 cells, cause eosinophilic inflammation, bronchoconstriction, and airway remodelling. Blood eosinophil counts are a potential surrogate biomarker for eosinophilic inflammation in asthma and are relatively easy to obtain. However, their levels depend on the time of sampling (highest at midnight, lowest at midday), time since eating, exercise, and therapy (corticosteroids reduce eosinophilia)[13]. Although studies of blood eosinophil count, as predictors of high

sputum eosinophils in eosinophilic asthma, have yielded somewhat mixed results, blood eosinophil counts have been useful in the selection of patients for eosinophil-targeting agents. The exact cut-off value is still debatable, but the cut-off used in the clinical trials to define high blood eosinophil counts has ranged between 150 and 300 cells/μL. Some studies showed that patients with eosinophil counts above 300 cells/_L have more frequent exacerbations and acute respiratory events[13].

Markers of Eosinophil Activation

The predominant mediators in the eosinophil granules are cytotoxic cationic proteins, such as eosinophil cationic protein (ECP), and eosinophil-derived neurotoxin (EDN), major basic protein (MBP), and reactive oxygen species (ROS). Some of these mediators can be measured in blood and used as a guide in better asthma clustering, but also as a potential treatment target. High ECP levels are detected in the blood and sputum of severe asthma patients (mostly atopic), compared to those with non-severe asthma. ECP is associated with bronchospasm and airway resistance and is elevated in asthma exacerbation, and its levels are reduced after therapy induction. It is assumed that ECP can be used as a marker for corticosteroid induction and dosage, but this needs to be confirmed. EDN is another marker of eosinophilic disease and persistent airflow limitation in severe asthma patients; it can be measured in serum, urine, and other body fluids[14-16].

Periostin

Periostin is an extracellular matrix protein secreted by bronchial epithelial cells and lung fibroblasts in response to Th2 cytokines, IL-13, and IL-4.

In addition to its role in cell proliferation, invasion and angiogenesis, periostin also plays a significant role in the development of inflammatory processes, as well as the development of the T2 phenotype[19,20]. The exact mechanism and role of periostin in the pathophysiology of asthma are still unclear. Mouse models suggest that periostin plays a role in mucus production, eosinophil recruitment, and subepithelial fibrosis.

In a recent study conducted by Takahashi et al., it was presented that serum periostin levels were good predictors of blood eosinophilia (r = 0.36), which could mean that periostin levels serve as a biomarker of eosinophilic airway inflammation[21,22].

50 ng/L is considered the cut-off in most studies while values above 50 ng/L are considered high periostin levels. The limitation of periostin is that it is also secreted by osteoblasts and the levels can be elevated in some tumours (brain tumours, bony metastasis), and growing children[23].

Dipeptidyl Peptidase-4 - DPP4

Dipeptidyl peptidase-4 (DPP-4) is expressed in a variety of lung epithelial and endothelial cells and submucosal glands, however, the role in the pathophysiology of asthma is uncertain. DPP-4 can be found in bronchoalveolar lavage (BAL) and correlates with airway inflammation in rat models. Studies related to DPP-4 are limited; IL-13 is thought to stimulate DPP-4 production, and, like periostin, DPP-4 can be measured in serum and can be used as a guide to induce anti-IL-13 therapy[18,24].

Immunoglobulin E

An utterly important predominant biomarker in patients with asthma is allergen specific IgE. IgE is a product of B lymphocytes in reaction to a foreign antigen[25]. Serum IgE levels have been shown to correlate with the severity of asthma. In the case of severe asthma exacerbations, total IgE levels rise, after which they fall, and stable levels are reached within 1-1.5 months after the onset of severe exacerbations[26]. Different specific immunoglobulin E and their interactions may be an important causal mechanism in the development

of asthma[27]. Nevertheless, with the advent of targeted asthma therapy, it gained a key role in tailoring individual therapy as well as monitoring its effectiveness. Depending on blood levels, total IgE may also indicate other comorbidities (including allergic bronchopulmonary aspergillosis, certain primary immunodeficiencies, infections and infestations (parasites), inflammatory diseases, and malignancies)[28].

Fractional Exhaled Nitric Oxide Concentration (FeNO)

Fractional exhaled Nitric Oxide (FeNO) is used to detect active airway eosinophilic inflammation, measured by solely non-invasive tests[35].

Due to its immense importance in the differential diagnostic process, fractional exhaled nitric oxide concentration (FeNO) has a distinctive role among all biomarkers. Nitric oxide (NO) is normally found in exhaled breath while patients with asthma often exhibit higher levels of NO in their exhaled breath, which is thought to be due to the upregulation of inducible nitric oxide synthase (NOS2) in airway epithelial cells, the enzyme in charge of epithelial NO production[36]. Given that NO levels can be measured relatively easily, and the test itself is non-invasive and easily repeatable, FeNO has enormous potential in everyday clinical practice.

The American Thoracic Society recommends clinically significant cut-off points for FeNO: (1) <25 ppb (<20 ppb in children), and (2) >50 ppb (>35 ppb in children)[37].

FeNO is a biomarker of T2 response (or airway eosinophilia) but does not correlate with sputum eosinophils. A FeNO level >50 ppb suggests a steroid-responsive inflammation, while patients with a FeNO level around 25 ppb are less likely to respond to steroids[37].

A recent study by Price et al., found that people with a combination of high FeNO and high blood eosinophils were prone to a notably increased risk of severe exacerbations in the year preceding FeNO measurement[38].

A recent study by Brooks, Massanari, Hanania and Weiner found that the implementation of FeNO into pre-omalizumab treatment assessment decreases the expected per-patient cost by almost 50% from the moment of omalizumab initiation into therapy, and the same trend continues during the first year of the omalizumab treatment. Authors point to the obvious benefit of using FeNO for detecting omalizumab responders (prior to initiating a 12-week trial of omalizumab)[39].

Induced Sputum and Airway Inflammation

Studies have demonstrated the usefulness of induced sputum to guide asthma treatment and showed that normalizing airway eosinophilic inflammation allowed better control of asthma with reduced exacerbations and hospital admissions[29]. The technique of induced sputum that allows non-invasive collection of airway cells is considered the gold standard to identify inflammatory asthma phenotype[30]. In one study performed using induced sputum, it was shown that compared to the paucigranulocytic phenotype, eosinophilic, neutrophilic and mixed granulocytic phenotypes were characterised by a poorer lung function. Eosinophilic phenotype exhibited a higher frequency of atopy, higher levels of IgE, higher bronchial hyperresponsiveness to methacholine, higher FeNO levels and lower asthma control compared to paucigranulocytic. The mixed granulocytic phenotype had higher levels of fibrinogen, the lowest lung function and the highest degree of bronchial hyperresponsiveness to methacholine[31]. As far as the sputum neutrophilic phenotype is concerned, there was a weak correlation between sputum and blood neutrophil count taken in percentage. In a study conducted by Ntontsi et al., it was found that paucigranulocytic asthma was most likely to be a benign asthma type, related to good treatment response[32]. Smokers did not have a significantly

higher proportion of neutrophils in their sputum than ex-smokers or never smokers[30]. Independent predictors of sputum eosinophil count ≥3% were the percentage of blood eosinophils, low FEV1/FVC, and high FENO and IgE levels. A cut-off value of 220/mm3 or 3% for blood eosinophils performed equally to FeNO50 ppb to identify the presence of a sputum eosinophil count ≥3%. Independent predictors of sputum neutrophilia were advanced age and high FRC, while blood neutrophil count was not[31]. *Sputum eosinophils >3% can only distinguish eosinophilic vs neutrophilic, mixed or paucigranulocytes asthma phenotype*[33]. Using blood eosinophilia per se as a biomarker for eosinophilic asthma is difficult due to the daily fluctuations of blood eosinophils, with or without treatment[34]. In the study by Agache et al., serum IL-5 and IL-13 were identified as the best blood eosinophilia predictors, with a good reproducibility at repeated testing after 6 weeks[34].

Conclusion

Asthma is a complex heterogeneous condition, and under this broad term, severe asthma itself covers several subgroups with specific characteristics, symptom profiles and biochemical mechanisms of the disease. A biomarker is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. In severe asthma, biomarkers could be used for diagnosis of phenotype or endotype, can also be predictive of clinical outcomes or response to therapy, and may be dynamic with time or therapy. Fully determining phenotype or endotype of severe asthma will require the interpretation of combinations of commercially available biomarkers. Today, defining a severe asthma endotype is a process based on a biomarker-driven approach. There is no perfect biomarker. Biomarkers for asthma are less precise, and still not completely known. With no perfect biomarkers, there is no perfect endotype classification. Multiple biomarkers are superior to a single biomarker. Despite significant improvement in asthma understanding, there is still a long way to go to resolve the asthma problem in most persons suffering from asthma syndrome.

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