

Allergology

Biomarkers in Allergic Airway Disease: Simply Complex

Adam M. Chaker^{a, b} Ulrich M. Zissler^{b, c} Martin Wagenmann^d
Carsten Schmidt-Weber^{b, c}

^aDepartment of Otorhinolaryngology and Head and Neck Surgery, Medical School, and ^bZAUM – Center of Allergy and Environment, Technical University of Munich, and ^cHelmholtz Center Munich, German Research Center for Environmental Health, Member of the German Center for Lung Research (DZL), Munich, and ^dDepartment of Otorhinolaryngology and Head and Neck Surgery, Heinrich Heine University Düsseldorf, Düsseldorf, Germany

Keywords

Biomarkers · Allergic airway disease · Component-resolved diagnosis

Abstract

Clinical diagnoses of allergic airway disease need confirmation of a relevant sensitization to allergens. Serum-based component-resolved diagnosis has become increasingly popular and allows the precise assessment of specific IgE to molecular allergens. Molecular allergen diagnosis has improved our understanding of disease phenotypes in allergic patients, including cross-reactive patterns and food allergy. Beyond sensitization profiles, characterization of the (endo-)type and severity of a local allergic disease is useful for targeted therapy with biologics in advanced allergic airway disease. Surrogate markers of treatment efficacy are increasingly under validation. Prognostic and predictive biomarkers will represent a promising option for stratified prevention strategies.

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Epidemiology and Background

Allergic rhinitis is the most common atopic disease and currently affects more than 600 million patients worldwide; the prevalence in Europe reaches approximately 25% [1]. According to recent data from population-based cohorts, sensitization to allergens as determined by specific serum IgE is present in more than 40% of the pediatric population in Germany [2]. Allergic rhinitis is a major risk factor for asthma [1, 3]. It impacts the quality of

Adam M. Chaker, MD
Department of Otorhinolaryngology and Head and Neck Surgery
Klinikum rechts der Isar, Medical School, Technical University of Munich
Ismaningerstrasse 22, DE–81675 Munich (Germany)
E-Mail adam.chaker@tum.de

life of affected patients and impairs sleep quality, outdoor activities, education, occupational performance, and driving skills [4–6]. Cutaneous types of efflorescence such as rash, hives, and eczema represent another major proportion of atopic disease [7]. The lifetime prevalence of self-reported food allergy in Europe is around 17% [8], but whether food has to be avoided or reintroduced [9, 10] is often beyond many otorhinolaryngologists' grasp. Even more drastic, severe, and threatening symptoms of distress and shock make patients suffer in the case of asthma or anaphylaxis [11]. Less than 10% of all patients in Germany receive adequate guideline-based treatment, and only 7% undergo specific immunotherapy [12], the only disease-modifying therapy available. Diagnostic procedures include skin testing and serum IgE; in the past decade, molecular allergen components including multiplex assays have increasingly been introduced [13].

The aim of this review is to briefly describe the advantages of the implementation of component-resolved diagnostics as daily used biomarkers in the field of allergic airway disease, which is often the responsibility of ENT specialists. A further aim is to provide an outlook on more sophisticated, new immunologic parameters.

IgE as a Biomarker for Allergy

The cornerstone of diagnoses of type 1 allergies is the verification of specific sensitization to an allergen and the correlation of this sensitization to the clinical symptoms of a patient. In clinical practice, validated skin prick test panels with standardized, extract-based allergens are used [14, 15]. They are simple, safe, and quick, but they can only be interpreted in the context of a patient's history. IgE not only is the key contributor to the pathophysiology of allergy but also serves as a biomarker: total IgE is indicative of overall allergic responses, and specific IgE permits the determination of sensitization [16]. IgE detection was further developed to detect molecular allergen components in order to better define patient profiles [17].

One straightforward example is an allergic patient presenting with a history of hay fever and mild, currently well-controlled allergic asthma mainly in the period from April to end of May in central Europe with a skin prick test positive for almost all seasonal allergens, from tree pollen and grasses to herbal allergens. Not few allergologists would advise this patient to refrain from allergen immunotherapy (AIT) due to a lack of potential for any benefit. In fact, these polysensitized patients are the ones that urgently require treatment beyond antihistamines and steroids [1, 18]. The diagnostic workup should consider the disparity between history and skin prick test. If available, nasal allergen challenges may prove useful. In any case, in vitro IgE testing should be included. Extract-based IgE testing would reveal the same pattern as a skin prick test. A suboptimal AIT concept may then be suggested for all tree pollen including ash, grasses, mugwort, and plantain, which – apart from reduced efficacy – would lead to higher costs, a higher risk of anaphylaxis, and the potential for additional iatrogenic sensitization.

Molecular allergen component IgE profiles allow for more accurate phenotyping also with regard to food allergy and anaphylaxis [19, 20]. This component-resolved diagnosis would yield the following results: Birch Betv1 Class 5, Grasses Phlp1&5 Class 1, Phlp4 Class 3, Plantain Plal1 Class 1, and Ash Ole1 Class 2. A stepwise approach for this patient would therefore comprise a 3-year, coseasonal, high-dose AIT for birch pollen, and, in preseason 2, the addition of a vaccine against ash to cover also major Ole1 allergens. The signal in the *Phleum* group would – consistently with the patient's history – mainly be ascribed to cross-reactive carbohydrate determinants, as Phlp4 is a highly cross-reactive marker for carbohydrate determinants, though a slight sensitization to major allergens is visible. The perspective

Table 1. Seasonal allergen components

Pollen	Specific	Cross-reactive
Birch	Bet v 1	Bet v 2 (profilin), Bet v 4 (Ca-binding protein)
Grasses	Phl p 1, Phl p 5, Phl p 2, Phl p 6	Phl p 12 (profilin), Phl p 7 (Ca-binding protein) Phl p4 (carbohydrate determinants)
Ash	Ole e 1	
Mugwort	Art v 1	
Ragweed	Amb a 1	
Plantain	Pla l1 (Ole1-related protein)	

Modified from Chaker and Klimek [21].

Table 2. Examples of candidate biomarkers for monitoring the clinical efficacy of allergen immunotherapy

Marker	Current status
Specific IgE/total IgE ratio and specific IgE/specific IgG4 ratio	Heterogeneous data, but well-established assays in routine practice [25, 26]
IgE-facilitated antigen binding	Promising, but only weak correlation with symptoms; transferable into routine clinical practice [24]
Intracellular diamine oxidase activation	Complex, intracellular fluorescence-activated cell sorter staining [28]
Cellular responses, enzyme-linked immunospot assay	Complex, cellular assays [27]

of AIT would be clouded in the case of evidence of profilin or polcalcin IgE (e.g., Betv2/4 and/or Phlp7/12). Since these were not detected in this patient, the recommendation would clearly be to start AIT. Over the course of 3 years, the symptoms of this patient would have to be monitored in a diary, and at the onset of symptoms during the grass pollen season starting end of May or June, *Phleum*-specific IgE should be reevaluated (Table 1; from Chaker and Klimek [21]).

Markers of Prognosis and Surrogates for Efficacy

The same patient would be interested to know whether his allergy is likely to become more severe. Based on clinical experience and stratified data available from clinical cohorts of children and adolescents (including machine learning approaches) the answer would be: probably yes. However, although distinctive markers or a combined set or algorithm of markers for specifying individual risks are not (yet) available, the data from cohorts already provide helpful information at least concerning children [22, 23].

If the same patient would now be interested in the efficacy of the AIT received, no molecular marker could currently be offered as a validated option for monitoring therapeutic responses and benefits. Often, epitope-specific IgG4 is considered to be a marker of AIT response, but it is rather a pharmacokinetic marker of the administered allergen without any correlation with symptom relief in individuals [24]. While IgE-facilitated antigen binding is

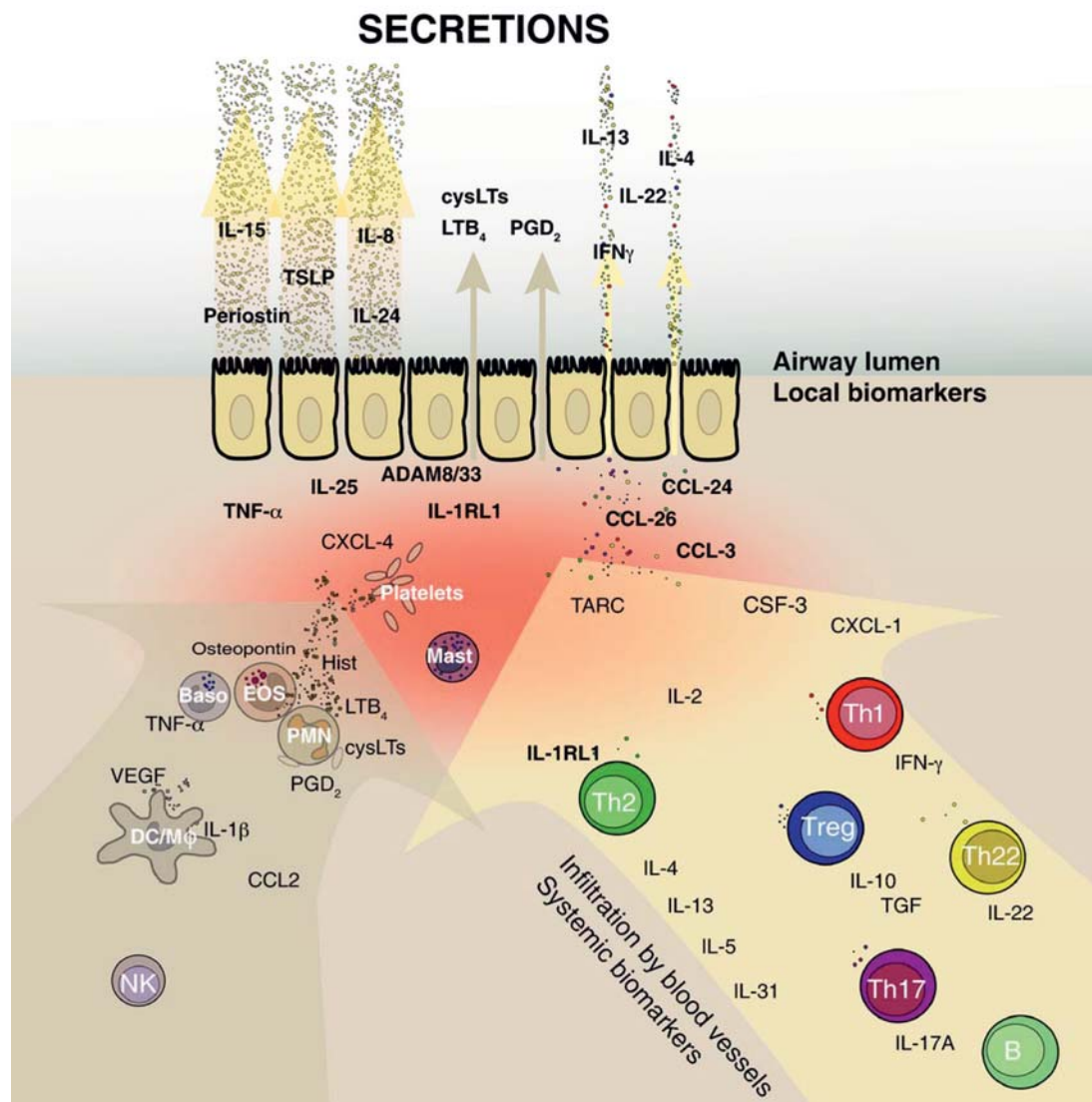


Fig. 1. Schematic overview of locally relevant biomarkers in the allergic airway, including luminally secreted mediators and mediators produced by submucosal infiltrates. Taken from Zissler et al. [29].

consistently robust and delivers modest correlations with the symptoms of patients [24], the situation of the specific-to-total IgE ratio [25] and the specific IgE/specific IgG4 ratio [26] is disadvantageous because of contradictory studies (see also Table 2). Titrated nasal and conjunctival allergen challenges can reveal a surrogate marker of efficacy as a clinical biomarker, but they are difficult to standardize and labor intensive. A complex and extensive systematic evaluation of biomarkers for monitoring the clinical efficacy of AIT has recently been performed by a task force of the European Academy of Allergology and Clinical Immunology (EAACI) and is likely going to be published in the first half of 2017 as a position paper. The most promising novel approaches include phenotyping of innate cell populations such as basophils and also the therapeutic monitoring of T-cell responses by means of enzyme-linked immunospot assays (ELISPOT) [27] and flow cytometry [28].

Outlook: Airway Mediator Endotyping

Acquisition of secreted local mediators from the nasal mucosa affords an exciting opportunity for endotyping patient groups based on the cytokine profiles of their secretions. These endotypes will also allow assessing individual risk profiles in children and help to identify high-risk patients based on their cytokine profile, perhaps even before the onset of sensitization [29], or to reveal prognostic information regarding ongoing sensitizations or a switch to asthma (*Etagenwechsel*) (Fig. 1).

The nasal sampling procedure is standardized, noninvasive, and well tolerated even by small children. In addition, also saline-induced sputa can be sampled to acquire lining secretions from bronchi in a noninvasive manner.

Apart from inflammatory cytokines, mediators such as periostin and osteopontin have been evaluated as markers of Th2 inflammation. Periostin seemed particularly suitable, as it proved to be useful in distinguishing responders to anti-IL-13 treatment [30] in a phase II study. However, phase III studies failed to confirm these data [31], and the potential of this particular stratification marker of allergic airway disease seems uncertain.

Allergic disease comprises allergen-specific, IgE-mediated reactions in its early phase and chronic inflammatory responses in its late phase. During natural allergen exposure, both phases overlap. To achieve the goal of restoring tolerance to an allergen in a sustainable way, we will need molecular approaches to control the inflammation at different hierarchical levels from epithelial to T- and B-cell responses in the affected tissues in addition to targeting the allergen. We will need complex clinical trials and endurance for establishing such procedures in clinical routine.

Disclosure Statement

The authors declare to have no competing interests.

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