



Precision/Personalized Medicine in Allergic Diseases and Asthma

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Abstract

Like many other chronic diseases, every allergic patient has different characteristics based on clinical course, treatment responsiveness and disease outcomes, which are associated with the genetic and epigenetic control of molecular mechanisms and environment. This variability necessitates the establishment of patient-tailored and precision approaches in handling allergic disorders. Better understanding of the underlying pathophysiological mechanisms for the development of allergic disorders will provide more rationale strategies based on individual cases in controlling and treating these disorders. Endotyping, phenotyping, genotyping and therotyping, and biomarkers are keywords in this area and have been gaining lots of attention in the field of precision medicine, which aims to revolutionize patient care and develop better prevention and treatment strategies. In addition, precision health is a new concept that brings precise approaches to the scene for being healthy and prevention of allergic disease and asthma. The specialty of allergy has a leading role in the field, because allergen-specific immunotherapy started 105 years ago, and is historically a leading personalized/precision medicine approach in all medicine disciplines providing the possibility of cure in an individualized manner instead of conventional symptomatic treatments.

Keywords Allergy · Asthma · Biomarker · Endotype · Phenotype · Theratype · Genotype · Cytokines · Precision medicine · Personalized medicine

Abbreviations

AIT	Allergen-specific immunotherapy
Breg	B regulatory
DC	Dendritic cells
Ig	Immunoglobulin
IL	Interleukin
ILC	Innate lymphoid cells
miRNA	MicroRNA
NK	Natural killer
SCIT	Subcutaneous immunotherapy
SLIT	Sublingual immunotherapy

Th	T helper
Treg	T regulatory

The Allergic Immune Response

The prevalence of allergic diseases has been remarkably increased during the last decades, and intensive work has been carried out for understanding the underlying mechanisms and developing new therapy regimens (Akdis 2015; Akdis et al. 2016; Bieber et al. 2016; Bousquet et al. 2012). Targeted and specific treatment strategies for individualized therapies are being extensively introduced for chronic non-infectious diseases as intentional approaches for management of chronic diseases, mostly being utilized as monoclonal antibody treatment regimens (Kucuksezer et al. 2013a; Ozdemir 2009, 2015; Ozdemir et al. 2016). Studies which aim to clarify underlying immune pathways of allergic disorders, as well as to figure out the unique roles of effector cells and molecular mechanisms will give power for developing new therapy strategies (Akdis and Akdis 2015; Akdis et al. 2016).

The genetic tendency to exhibit hypersensitivity reactions to ubiquitous environmental allergens in an immunoglobulin

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(Ig) E type antibody-dependent manner under the influence of microenvironment is termed as atopy (Larche et al. 2006; Platts-Mills et al. 2016). Allergens including certain aero and food allergens and insect venoms have capacity to induce clinical symptoms in sensitized atopic individuals. When these allergens are presented in skin or mucosal surfaces of genetically susceptible individuals, they are internalized by antigen-presenting cells, mainly by dendritic cells (DCs), which are professional antigen-presenting cells specialized for presentation of antigens to immune cells, mainly to CD4⁺ T-cells (Muehling et al. 2017). DCs are activated following allergen encounter and start migrating to lymph nodes, where the presentation of the T-cell epitope peptides of already processed allergens to naïve T-cells, together with co-stimulatory signals takes place. As a consequence, activated T-cells start to differentiate into T helper (Th)2 type cells in atopic people, which consequently start to produce Th2-type cytokines like interleukin (IL)-4, IL-5, IL-9 and IL-13, the cytokines contributing to atopic diseases (Akdis et al. 2016). IL-4, as well as IL-13 are known to trigger class switching of B-cells to produce IgE, which have capacity to bind to high-affinity IgE receptors (Fcε) located on mast cells, basophils, as well as eosinophils, the effector cells of allergic inflammation. These cells are termed to be “sensitized to that individual allergen” when allergen-specific IgE is bound to Fcε receptors of these effector cells (Lawrence et al. 2017; Oettgen 2016; Platts-Mills et al. 2016).

When a sensitized individual is exposed to this particular allergen, sensitized effector cells, such as mast cells and basophils immediately discharge their pre-formed mediators positioned in their granules. In addition, the production of new biogenic mediators like histamine, proteases, lipid-derived mediators like leukotrienes and also cytokines are initiated, all of which are known to be responsible from symptoms and signs of allergic type 1 hypersensitivity reactions (Platts-Mills et al. 2016). Of Th2 cytokines, IL-5 has imperative roles on recruitment, activation and survival of eosinophils, together with B-cell growth. IL-13 was shown to contribute to epithelial cell maturation and production of mucus, contraction of smooth muscle of airways and generation of extracellular matrix proteins (Wills-Karp et al. 1998). The cytokines produced by effector cells of allergy have roles to play on increase of vascular permeability, fibrosis, angiogenesis and promote infiltration of basophils, eosinophils, macrophages, neutrophils and T-cells, all are known to contribute to augmentation of late phase responses, which are attributed to be reasons for persistent, chronic signs and symptoms of allergy (Akdis et al. 2004) (Fig. 1).

Recent Advances in Immunology of Allergic Diseases

It is of great importance to understand the most recent progresses in field of allergic inflammation and immunology to develop novel ways of precision medicine in the field.

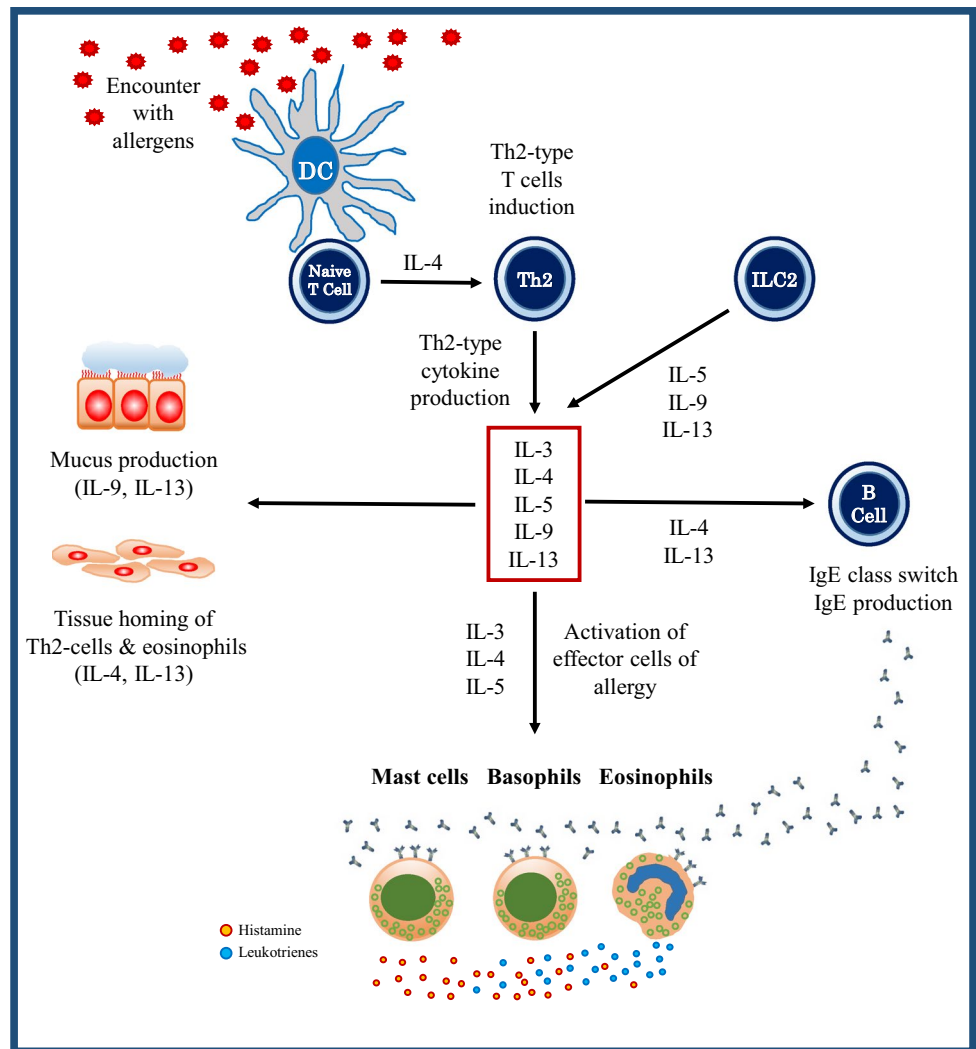
Innate Lymphoid Cells

Innate lymphoid cells (ILCs) are recently defined as lymphocyte subsets, which are known to lack T- and B-cell antigen receptors and lymphoid and myeloid lineage markers. These cells were claimed to control mucosal environment both by production of cytokines and chemokines, and by close communication with epithelial and other tissue cells (Doherty et al. 2015; Nagakumar et al. 2016; Nagarkar et al. 2015). Three subsets of ILCs, with similarity to Th-cell subsets are defined; ILC1 is known to produce interferon γ , ILC2 is capable of producing IL-5 and IL-13, while ILC3s produces IL-17 and IL-22 (Annunziato et al. 2015; Doherty et al. 2015; Mjosberg and Spits 2016). ILC2 were claimed to contribute to development of allergic diseases, by their similar cytokine production patterns to Th2 cells (Salimi et al. 2013). They receive IL-25 and IL-33 signals from epithelial cells and get activated (Jackson et al. 2014; Mjosberg and Spits 2016; Morita et al. 2015; Ozyigit et al. 2015). A study reported increased counts of ILC3 together with ILC2 in grass pollen allergic patients, during the pollen season (Lombardi et al. 2016). Although there are studies reporting changes of proportions of ILC subsets in response to allergen-specific immunotherapy (AIT), intensive studies are required for revealing contribution of ILC subsets either in allergy pathogenesis and its regulation.

Regulatory T-Cells

Immunological tolerance is critical for dampening inflammatory reactions both to infections and to innocuous environmental antigens, which are important for prevention of chronic inflammation as well as tissue damage (van de Veen et al. 2016). Intensive research in last 20 years has contributed to understanding cellular and molecular mechanisms of immune tolerance to allergens, in humans. Substantiation of T-cell tolerance facilitated by IL-10 was an important milestone in this area. Generation of allergen-specific T- and B-cell subsets, secretion of immune-suppressive factors, IgG4 production and functional down-regulation of mast cells, basophils and also eosinophils are essential constituents of the immune tolerance network (Akdis and Akdis 2014a) (Fig. 2). Different subsets of regulatory cells exist, including T regulatory (Treg) cell subsets, B

Fig. 1 Basic mechanisms of allergic inflammation. When environmental allergens are encountered by dendritic cells (DCs), they are uptaken, processed to peptides and are presented to naïve CD4⁺ T-cells. With the presence of IL-4 in the milieu, induction of Th2 cells and production of Th2-type cytokines, namely IL-3, IL-4, IL-5, IL-9 and IL-13 are initiated. B-cells class switch and begin to produce IgE-type antibodies against allergens, which in turn binds to specific Fcε receptors on mast cells, basophils as well as eosinophils; namely the effector cells of allergic inflammation. This context is termed as “sensitization” and whenever these cells face the same allergen, mast cells and basophils instantaneously degranulate, which consequently leads to secretion of histamine and leukotrienes all of which brings about immediate hypersensitivity. Th2-type cytokines are responsible from mucus production and also from tissue homing of eosinophils and also Th2 cells. Type-2 Innate lymphoid cells (ILC2) contribute to allergic inflammation by production of Th2-type cytokines



regulatory (Breg) cells, natural killer (NK) cells and ILCs. Different T-cell subsets having suppressive capacity form Treg cells, which limit development of allergic inflammation by various ways of action, including production of suppressive cytokines and inhibition by surface molecules. Mechanisms of Treg cell generation and the identification of novel immune organs, where Treg generation in vivo occurs, like tonsils, are recently being elucidated (Palomares et al. 2014). The studies investigating healthy immune response to allergen exposure in cat owners, as well as in beekeepers revealed induction of IL-10-producing type 1 Treg cells, which were claimed to have important contributions to outcomes of AIT (Akdis and Akdis 2015, 2014b).

Breg cells are gaining importance nowadays, though being previously under focus in 1970s, as a consequence of allergen sensitization studies (Katz et al. 1974; Neta and Salvin 1974). Recent studies revealed that IL-10, IL-35, as well as transforming growth factor β contribute to immune suppression by Breg cells, together with production of IgG4

by them, which have non-inflammatory functions with the aspect of atopic diseases. Several sub-types of Breg cells have been discovered and in vivo existence of these cells are proven by increased expression during AIT, as well as in high-dose allergen exposed beekeepers. These findings underline possible roles of Breg cells in mediation of allergen-specific tolerance (van de Veen et al. 2016). According to a recent study, when IL-10-transfected human B-cells overexpress IL-10, they were revealed to acquire an immune-regulatory profile, with increased suppressor molecules such as programmed death ligand 1 and CD25, IL-1 receptor antagonist and vascular endothelial growth factor, and with diminished production of proinflammatory cytokines, tumor necrosis factor α , macrophage inflammatory protein 1 α and IL-8, together with diminished production of IgE. These cells were claimed to suppress production of proinflammatory cytokines from peripheral blood mononuclear cells, DC maturation and antigen-specific lymphocyte proliferation in vitro (Stanic et al. 2015). Recently, a

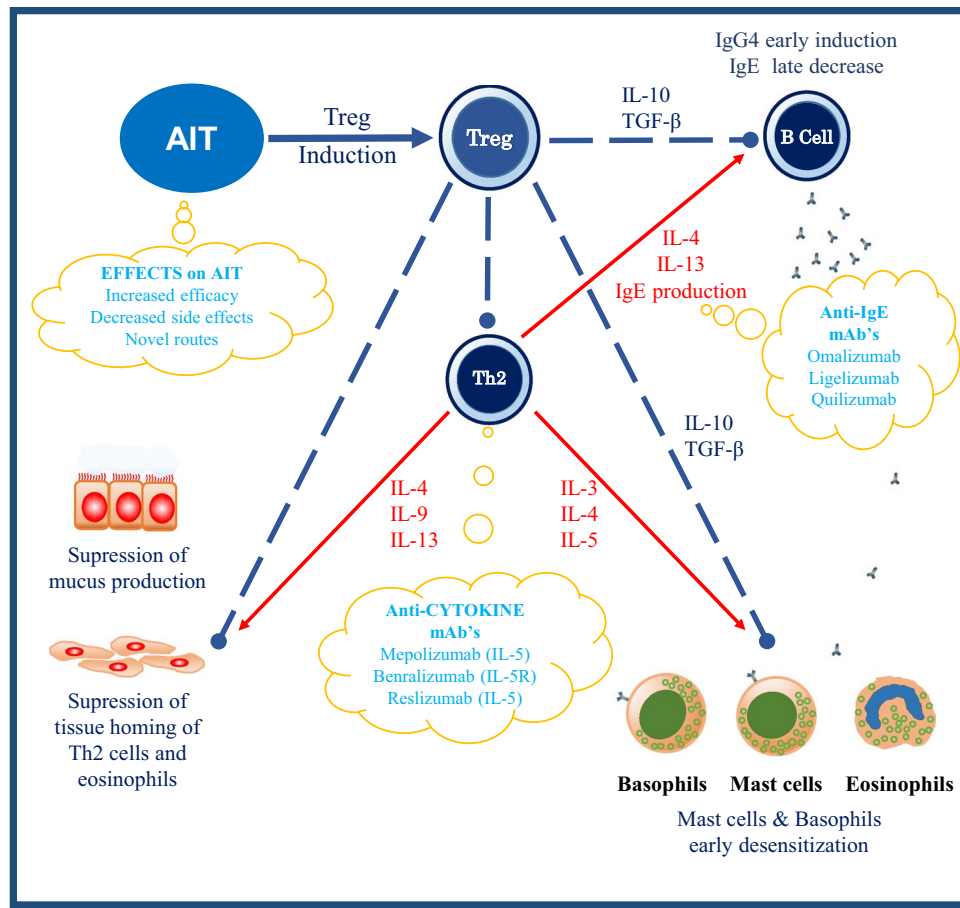


Fig. 2 Immune-regulatory mechanisms by T-cells in allergy. A specific T-cell subset with suppressive capabilities is termed as regulatory T (Treg) cells, which can be induced as a consequence of both allergen-specific immunotherapy (AIT) and natural exposure to allergens in a high-dose manner. These cells' suppressive ability is the result of possession of direct inhibitory surface molecules contact or production of inhibitory cytokines like IL-10 and TGF- β . Treg cells suppress Th2 cells, induce class switch of B-cells from allergic IgE isotype to non-inflammatory IgG4 isotype, desensitize effector cells

of allergy and suppress both mucus production and also homing of Th2 cells and eosinophils to tissues. Precision medicine has important offerings to allergy regulation, by enhancing efficacy of immunotherapy or by binding to important molecules of allergic inflammation like IgE and IL-5. In figure, red arrows represent pathways of allergic inflammation, dashed blue arrows indicate inhibitory effects of AIT, while cloud-type boxes represent targets of precision medicine on regulation of allergic inflammation

link between CD40L-expressing ILC3 and IL-10⁺ Breg cell induction has been demonstrated in human tonsils (Komlasi et al. 2017). Briefly, both Treg and Breg cells are claimed to have roles together in suppression of IgE production and class switch to allergen-specific IgG4, mediated by IL-10. NK and NKT cells expressing high levels of IL-10 as well as DCs were also claimed to contribute to healthy immune response to allergens (Palomares et al. 2014).

Dendritic Cells

Dendritic cells are important sentinels of immunity, bridging innate and adaptive immune responses, and have indispensable roles both in induction and regulation of T-cell

immunity, a key step in initiation and regulation of allergic diseases (Kucuksezer et al. 2013b). Immature DCs are shown to polarize into DC1, DC2, DC17 and DCreg cells, which in turn are revealed to initiate T-cell differentiation into Th1, Th2, Th17 and Treg, respectively. These DC subsets are shown to express some subset-specific markers, which may have importance in discrimination between allergic or tolerogenic effects (Gueguen et al. 2016). Targeting specific DC subsets to induce allergen tolerance has been one of the aims for novel vaccine development for AIT (Sirvent et al. 2016). Taken together, intensive investigations and their contributions to the field have been focused on the development of new therapy strategies dependent on these cell subsets as well as their products.

Personalized Medicine in Allergy and Asthma

A Need for a New Nomenclature

Allergic disorders have an important socioeconomic impact, due to their chronic nature, inadequate diagnosis and incompetent treatment (Ferrando et al. 2017). Although, there is one disease; allergy, patients present with different stories, different underlying molecular mechanisms with accompanying disease outcomes, all of which are the influences of genetic background and epigenetic control of molecular mechanisms by the rapidly changing environment. In this rapidly developing area, there is an important need for the specialty to develop new nomenclature to better identify clinical conditions related to personalized medicine. Endotype, phenotype, theratype and biomarker terms delineate major keywords in precision/personalized medicine (Agache et al. 2012; Akdis et al. 2013; Akdis and Ballas 2016). An endotype is a disease form defined by a distinct pathology related to a molecular mechanism. A disease phenotype is an evident characteristic of a disease with no focus on the underlying mechanism. A theratype defines clinical responders to a specific therapy. A biomarker is used for examination of any pathogenic or biological process, which may be used for main biological aspects of a diagnosis, patient selection, response to therapy side effects, etc. (Agache et al. 2015; Bachert and Akdis 2016; Berry and Busse 2016; Muraro et al. 2016; Werfel et al. 2016). In the field of clinical usage of biologics for custom-tailored therapies, the knowledge should be deepened with further investigations on biomarkers specific for newly developed biologics (Bleecker et al. 2016; Ferrando et al. 2017) (Table 1).

Type 2 Immunity Represents a Complex Endotype in a Majority of Allergic Patients

Type 2 immune response comprises Th2 cells, type 2 B-cells, group 2 ILCs, IL-4 secreting NK as well as NKT cells, eosinophils, basophils and mast cells and their key cytokines (Agache and Akdis 2016; Agache et al. 2015). IL-4, IL-5, IL-9, and IL-13 are produced mainly by the cells of the immune system, while IL-25, IL-31, IL-33 and thymic stromal lymphopoietin are mainly secreted from tissue cells, particularly epithelial cells and all form a complex network (Akdis et al. 2016). Several endotypes and theratypes may be present within the complex type 2 endotype, as IL-5-high, IL-13-high or IgE-high endotypes, and their predominance diverges between atopic disorders. Although in general, type 2 complex endotype is known to

be a well-responder to inhaled corticosteroids, anti-IL-5, anti-IL-4, anti-IL-13 and anti-IgE responsive theratypes are present, all of which remain to be further elucidated.

Development of Biomarkers

Biomarkers in allergic diseases and asthma are gaining importance, day by day. As there is still no single biomarker sufficient enough to be used as a gold standard, it is necessary to use a combination of biomarkers for improvement of disease management. Novel biomarkers have to be identified from studies investigating cells and immune networks underlying allergic inflammation, and they should demonstrate theratypes by discriminating therapy responders from non-responders. This is particularly necessary for expensive therapies such as biologics and AIT that continues for several years and the discovery of biomarkers would be exceptionally valuable in many aspects such as:

- identifying patients, who will benefit from the treatment,
- monitoring during and after the treatment,
- adapting immunization schemes and dosing,
- inaugurating biological mechanisms of action of efficacious immunotherapy,
- supporting the authorization process for a treatment or a drug,
- prediction of side effects,
- prediction of long-lasting protection,
- improve acceptance of a specific therapy,
- improve patient compliance.

Several biomarkers have been projected for monitoring of allergic inflammation (e.g., eosinophil numbers or levels of eosinophilic cationic protein in sputum, nasal fluid tryptase levels) (Konig et al. 2015). Periostin is a protein of the extracellular matrix, which is known to be upregulated in response to IL-4 or IL-13, and serum levels of periostin relate to type-2 inflammation and also lung function in asthma. Serum periostin levels were found elevated in children with asthma (Inoue et al. 2016). It has recently been reported that periostin in serum could also serve as a biomarker for both eosinophilic airway inflammation and also for fixed airflow limitation in well-controlled asthmatics (Takahashi et al. 2018). Serum periostin was found to be positively related with increased nitric oxide, and total IgE, whereas an inverse relationship with lung function was observed in patients with asthma (James et al. 2017). Another non-invasive and indirect biological quantification way of airway hyper reactivity is nitric oxide content in exhaled air (Anderson and Szeffler 2015). All these mentioned markers relate to inflammatory symptoms linked with late immune effector mechanisms, and as such are likely to be relevant to follow up the impact of

Table 1 Major clinical trials placed in <http://www.clinicaltrials.gov> with respect to allergic diseases and precision medicine

Identifier	Title	Aim	Recruitment status	Patient group	Intervention	Published
NCT01681732	A Pilot Study of Personalized Medicine for Pediatric Asthma	To test the feasibility of a personalized asthma care intervention	Completed	6–17 years old, pediatric asthma patients	Personalized asthma management	No
NCT01196377	Personalized Medicine, Biomarker-based Study of Optimal Albuterol Regimens for Acute Asthma Exacerbations: DBRCT Pilot Study	To model a pediatric acute asthma clinical decision rule for personalized medicine by identification of phenotypes within the frame of therapy response phenotypes	Completed	5–17 years old, pediatric asthma patients	Nebulized albuterol	No
NCT01027143	Obesity and Asthma: Nutritional Response to Omega-3 Fatty Acids	To assess the efficacy of omega-3 fatty acid supplementation for asthma symptom control and in obese asthmatics, investigation of genetic influence on treatment response. Better understanding of the link between obesity and asthma	Completed	12–25 years (pediatric and adult) Asthmatic and obese patients	Omega-3 fatty acid as dietary supplement or as drug	No
NCT01928771	A Multicentre, Randomized, Double-blind, Parallel Group, Placebo-controlled, Phase III Efficacy and Safety Study of Benralizumab (MEDI-563) Added to High-dose Inhaled Corticosteroid Plus Long-acting β_2 Agonist in Patients With Uncontrolled Asthma	To determine if benralizumab has capacity to reduce asthma exacerbation numbers in patients who remain uncontrolled on high doses of ICS-LABA	Completed	12–75 years (pediatric, adult and older adult) asthmatic patients	Benralizumab versus placebo	Bleecker et al. (2016)
NCT01346852	Predictive Ability of Therapeutic Risk Factors in Pediatric and Adult Asthma Patients	To assess the predictive ability of three asthma risk markers: the ratio of controller medication to total asthma medication, an albuterol only marker, and an oral corticosteroid use marker, as well as to compare the precision of these tools between adult and pediatric patient populations	Completed	4–17 years pediatric asthmatic patients 18 years and older adult asthmatic patients	An asthma-related medication and an asthma controller medication	Not provided

symptomatic treatments such as corticosteroids or antihistamines. However, AIT is a therapy option aiming to correct the immune imbalance present in allergic patients (from a Th2 to Th1 or Treg cell response) in an allergen-specific fashion (Chung 2015). Therefore, a biomarker for AIT will reasonably likely to be involved in the alteration of an immune parameter reflecting the early origin of inflammation.

Several approaches for the discovery of novel biomarkers are being taken such as short, single-stranded RNA molecules, named as microRNAs (miRNAs) were discovered in last decades. MiRNAs are claimed to silence genes by inhibition of translation or degradation of target miRNAs, by functioning together with proteins and targeting hundreds of genes. MiRNAs can be present extracellularly in body fluids and were claimed to be involved in cell to cell communication (Rebane and Akdis 2013). A recent study investigating contribution of miRNAs to allergic inflammation reported suppression of chronic skin inflammation in atopic dermatitis by miRNA-146a, by inhibition of a number of inflammatory factors by a nuclear factor kappa B-dependent manner (Rebane et al. 2014). MiRNAs may have the capacity for being used both as a biomarker and as novel treatment modalities in allergic diseases.

Limitations on the Way to Define Biomarkers

The extremely low rate of allergen-specific T- and B-cells that are responsible for allergen-specific immune responses is the major limiting factor for the biomarker discovery. They represent less than 0.01% in many cases and it is practically very difficult to demonstrate them. MHC class-II tetramer staining for T-cells and allergen-labeled B-cells can be used to purify these cells; however, these are sophisticated techniques that can only be performed in highly equipped and skilled laboratories. The other important limitations are listed below (Boonpiyathad et al. 2017; Zaleska et al. 2014):

- Very low frequency of T-cells specific for a certain allergen,
- Very low frequency of allergen-specific B-cells,
- Difficulties in feasibility, material transport, time, costs,
- Difficulties in handling expertise of cellular assays with T-cells, B-cells, basophils,
- Low number of samples and individuals so far tested,
- No changes in specific IgE due to long living established IgE memory in bone marrow,
- Success in individual patients does not always depend on immunological parameters (i.e., mastocytosis, multiple allergies, combined nonallergic inflammation),
- No human method to analyze mast cells.

Characteristics of a Good Biomarker

- Easy determination including point-of-care,
- Should be detected in easily accessible whole blood, serum, body fluids,
- Should not include difficult to perform cellular assays,
- Should respond to all questions above related to better patient care,
- No requirement for cell cultures,
- Should be cost efficient.

Theratype, a Decisive Patient Classification in Personalized/Precision Medicine

As multiple mechanisms together with various triggers underlie the pathogenesis of atopic disorders such as allergy, asthma, atopic dermatitis and chronic rhinosinusitis, a single and general therapy option seems not to be applicable for the entire patient population (Bachert and Akdis 2016; Muraro et al. 2016). Identification of a specific therapy response, namely therotyping is greatly important, which has potential for establishment of better disease prevention and better patient care as well. In this context, precision medicine approaches with novel biologics are emerging (Durham and Penagos 2016; Werfel et al. 2016). With increased contribution of precise medicine in allergy, one may expect to better define treatment responders, design disease-modifying strategies and reduce risks associated with therapies (Akdis and Ballas 2016; Galli 2016) (Table 1).

Safety and efficacy of targeted therapy are the main issues in considering the prescription of these drugs. As targeted therapy is more expensive than today's conventional interventions, decision of their prescription in selected patient groups should be given based on needs, past treatment history, response to conventional treatments and characteristics of the patient. Considering the length of the treatment, calculation of total treatment costs is mandatory.

IgE was targeted by the initially developed biologic drug in the field of allergy, omalizumab, a humanized IgG1 monoclonal antibody which has the capability to bind to circulating IgE, and consequently blocks IgE binding to its receptors present on mast cells and basophils (Fig. 2). This blockade is claimed to end up with decreased degranulation of mast cells and basophils and decreased release of mediators of allergic inflammation (Baird et al. 1989). This biologic is revealed to be efficient and safe in controlling allergen-dependent airway inflammation and also has significant capacity to reduce exacerbation numbers while providing significant benefits in allergic asthmatic children (Busse et al. 2011; Ferrando et al. 2017; Sorkness et al. 2013). Omalizumab is still the first drug to target a specific sub-group of asthmatic patients and is claimed to have possible contributions to other IgE-related diseases like allergic rhinitis, chronic

urticaria, atopic dermatitis and food allergies (Ferrando et al. 2017) (Table 2). Omalizumab is recommended as an add-on therapy option for patients aged ≥ 6 years with moderate to severe allergic asthma which is uncontrolled on Step 4 treatment of the report of Global Strategy for Asthma Management and Prevention 2018 update of Global Initiative for Asthma (GINA Report 2018; Roberts et al. 2018). Also, it has been suggested that patients may benefit from omalizumab therapy in phenotype-guided add-on treatment for patients ≥ 6 years with severe allergic asthma with elevated levels of IgE (Normansell et al. 2014; Rodrigo and Neffen 2015). Omalizumab is titrated according to the total serum IgE level.

Two other biologics with anti-IgE activity, namely ligelizumab and quilizumab are also being developed (Arm et al. 2014; Gauvreau et al. 2014). Exploration of important contribution of IL-5 and eosinophils to pathogenesis of asthma focused attention on IL-5 and biologics targeting IL-5 were developed (Fig. 2). Mepolizumab targeted IL-5, and clinical trials reported various efficacy levels, however, when patients were selected attentively, keeping eosinophil counts in mind, a significant reduction in acute exacerbation frequencies together with dropped eosinophil counts and decreased corticosteroid needs were observed (Bel et al. 2014; O'Byrne et al. 2001; Pavord et al. 2012). These findings on the other hand underline eosinophil counts as a possible important biomarker. Reslizumab, an anti-IL-5 drug that has been approved in severe adult eosinophilic asthma and benralizumab is an anti-IL-5R monoclonal antibody in development for treatment of patients with severe asthma (Castro et al. 2014, 2015). In the above-mentioned GINA report (2018), anti-IL-5 interventions have found place for patients with severe eosinophilic asthma which are uncontrolled on Step 4 treatment. For these selected patient groups, add-on treatment of subcutaneous mepolizumab is given for patients aged ≥ 12 years, which is administered once a month at a single dosage. Intravenous reslizumab for ages ≥ 18 years as well as anti-IL-5 receptor treatment with

subcutaneous benralizumab for ages ≥ 12 years are recommended (Castro et al. 2015; Halder et al. 2009; Nair et al. 2017; Pavord et al. 2012; Wang et al. 2016).

IL-4 is a vital cytokine in differentiation of naïve Th cells into Th2 cells and stimulates activation of B-cells, which enroll in allergen-specific IgE synthesis. Dupilumab is the human monoclonal antibody that binds to IL-4R α , which inhibits the biological activity of both IL-4 and IL-13. Dupilumab has been already used and approved in the cure of the adult patients with moderate to severe atopic dermatitis (Beck et al. 2014).

On the other hand, AIT is the standard way of long-term cure of allergic diseases, by induction of allergen-specific tolerance (Fig. 2). The effect is gained by administering standard amounts of the sensitized allergen to the patient for a long time, induction of allergen-specific Treg cells as well as recently defined innate-type lymphoid cells, and induction of tolerant-type IgG4 isotype antibodies (Akdis et al. 2004; Ozdemir et al. 2011; Shin et al. 2018). Two standard methods of AIT are subcutaneous (SCIT) and sublingual (SLIT) routes of immunotherapy. Both SCIT and SLIT are revealed to be beneficial, however, some patients' response to treatment are not as good as the others (Tabatabaian and Casale 2015). Alterations in cellular responses and also in cytokine profiles were claimed to be possible novel biomarkers for determination of AIT efficacy, though still with more room for improvement (Kouser et al. 2017). AIT was also claimed to have possible limiting effects on development of new allergen sensitizations (Di Bona et al. 2017).

There are a great numbers of studies, which aim to improve efficacy of AIT routes and to decrease associated side effects (Bonertz et al. 2018; Curin et al. 2018; Hoffmann et al. 2017; Pohlitz et al. 2017; Soria et al. 2018). As an example, a study aimed to erase B-cell epitopes and avoid IgE cross-linking but to protect T-cell epitopes and reported a fusion protein of two major bee venom allergens: phospholipase A 2 (Api m 1) and hyaluronidase (Api m 2), by genetic engineering, which resulted in induced T-cell proliferation,

Table 2 Some published recent monoclonal antibody clinical trials with promising results in major clinical outcomes

References	Drug of interest	Patient population	Major outcomes
Bhutani et al. (2017)	Omalizumab	Moderate to severe allergic asthma	Reduction in total oral corticosteroid use and exacerbation frequency, improved asthma control and quality of life
Lee et al. (2018)	Omalizumab	Severe asthma	Reductions in asthma exacerbations, hospitalizations, hospitalization days, systemic corticosteroid requirements, and sputum eosinophil count
Shimoda et al. (2017)	Mepolizumab	Severe eosinophilic asthma	Exacerbations were reduced, increased morning PEF, improved quality of life, reduced eosinophil counts
Chupp et al. (2017)	Mepolizumab	Severe eosinophilic asthma	Improvements in Health Related Quality of Life
Liu et al. (2013)	Mepolizumab	Asthma	Reduces risk of exacerbations and improves quality of life in patients with eosinophilic asthma, no significant improvement in lung function outcomes

abolished IgE reactivity, and decreased basophil reactivity (Kussebi et al. 2005), all of which are beneficial for outcomes of a successful AIT.

Better characterization of allergens is greatly important for improved success of AIT. As an example, Amb a 1, the major allergen of ragweed pollen extracts is claimed to have five different isoforms, each possessing distinct patterns of immunogenicity and sensitizing assets. These different properties of each isoforms should carefully be taken into account from development of diagnostic tests to utilization for ragweed AIT (Wolf et al. 2017). Although, there is a necessity for larger, randomized, placebo-controlled trials, combinational usage of omalizumab with AIT has been reported in several clinical trials for allergic rhinitis, as well as in oral immunotherapy trials for peanut, egg and cow's milk allergy, and show promising results with respect to increased efficacy and safety (Dantzer and Wood 2018; Lin et al. 2017; Massanari et al. 2010). Also, several case series, which report completion of the maintenance phase under omalizumab in patients, have experienced recurrent anaphylaxis with bee venom immunotherapy (Schulze et al. 2007). It is likely that experimental studies aiming to increase efficacy of AIT are on the way; as an example, in a recent murine model, combined use of SLIT with anti-IL-2 monoclonal antibodies in mice reported reversal of IgE-mediated allergy and increased Treg-mediated tolerance to allergens, which may be a fruitful modification to AIT (Smaldini et al. 2018).

Better understanding of the allergy phenotypes is of great importance for development of custom-designed therapies unique for each patient. For improved success of immunotherapy, selection of patients for each AIT is being discussed nowadays (Agache 2018; Pfaar et al. 2018; Roberts et al. 2018; Tabatabaian and Casale 2015). Biomarkers for patient selection and as early predictors of responders are being questioned nowadays (O'Mahony et al. 2016; Su et al. 2018). Customization of AIT by means of precision medicine is expected to help for election of patients who have potential to benefit from AIT or biologics and selection of correct allergens for AIT (Muraro et al. 2017; Yii et al. 2018). It is clear that efficacy of AIT can be improved by precision medicine methods.

Conclusion

With precision medicine, it is possible to manage allergic disorders in a better way as individualization of the patient care will enable improved diagnosis and prognosis, which will lower treatment costs, and will provide better assortment of treatment responders, and thus better projection of disease-modifying and prevention strategies.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflict of interest.

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