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IgE-associated allergic disorders: Recent advances in etiology, diagnosis and treatment

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Abbreviations:

ACD	Allergic Contact Dermatitis
AD	Atopic Dermatitis
AR	Allergic Rhinitis

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ASST	Autologous Serum Skin Test
BAT	Basophil Activation Test
Bet v 1	Birch Pollen Allergen
CSU	Chronic Spontaneous Urticaria
DCNB	Dinitrochlorobenzene
DOCK8	Dedicator of Cytokinesis 8
EPIT	Epicutaneous Immunotherapy
FcεRI	High Affinity IgE Receptor
FcγRIIb	Low Affinity IgG Receptor IIb
CS	Corticosteroid
HDM	House Dust Mite
HIES	Hyper IgE Syndrome
HMO	Human Milk Oligosaccharide
HR	Histamine Receptor
IFN-γ	Interferon γ
Ig	Immunoglobulin
IL	Interleukin
PI	Parasite Infection
PP5	Protein Phosphatase 5
SCIT	Subcutaneous Immunotherapy
SCRAD	SCORing Atopic Dermatitis
SIT	Specific Immunotherapy
SLIT	Sublingual Immunotherapy
TLR	Toll-like Receptor
TSLP	Thymic Stromal Lymphopoietin
TRPA1	Transient Receptor Potential Channel Member A1
UAS7	Urticarial Activity Score for 7 days

Abstract:

IgE-associated allergic diseases belong to the most common inflammatory conditions. Their clinical manifestation ranges from mild symptoms to life-threatening episodes. Often patients experience a reduction in physical and psychologic well-being and suffer from a decreased quality-of-life due to disease activity. The continuously rising number of people that are affected by an allergic condition indicates an urgent need for better diagnostics and more efficient treatment options. Recent progress in the understanding of pathophysiologic mechanisms underlying IgE-associated allergic disorders have led to the identification of novel therapeutic targets and the development of drug candidates that are currently under evaluation. In this review, we highlight studies and clinical trials, which have helped to gain further insight in the etiology of IgE-associated allergic conditions as well as advances in the development of diagnostic tools and therapeutic approaches recently published in the *European Journal of Allergy and Clinical Immunology*.

Since the discovery of immunoglobulin E (IgE) in 1967 it has become increasingly evident that this antibody plays an essential role in allergic diseases. Even though IgE is the least abundant antibody in human serum it has the ability to induce potent inflammatory immune responses in various tissues and organs. The serum levels of total IgE, however, rarely provide information about the amount of allergen-specific IgE and the presence of specific IgE does not necessarily translate into a clinically meaningful response to the corresponding allergen. Over the last decades, researchers and physicians have learned that the contribution of IgE to the etiology of allergic disorders may considerably vary (Fig. 1) and that other parameters might be equally important in the pathogenesis. In the following section we will summarize recent findings on IgE-dependent as well as IgE-independent mechanisms associated with allergic disorders.

1. IgE-Associated Allergic Disorders

1.1 Allergic Asthma

Asthma is a chronic inflammatory airway disease, which can be elicited by a variety of environmental substances. Worldwide, an estimated amount of 300 million people are suffering from this respiratory condition (1,2). Allergic asthma, which is often induced by pollen, dust mite or mold-derived allergens during childhood, represents the most common type of asthma. A study assessing IgE responses (i.e. sensitization) against food and inhalant allergens in a pediatric population that has been prospectively followed for 16 years reports that 51% of children have been tested positive for allergen-specific IgE at least once during this period (3). However, 23% of sensitized children did not experience allergic asthma. Nevertheless, the authors state that specific IgE is strongly associated with the development of asthma from an age of 4 years. Additionally, the sensitized group of children that did not develop asthma was characterized by less parental allergy occurrence, suggesting that genetic factors play an important role in disease manifestation. Another study summarizing data from five geographically distinct European birth cohorts has reported that moderate and high house dust mite (HDM) bedroom concentrations correlated with an increased prevalence of HDM sensitization up to 6 years of age (4). However, no significant associations were detected between high and low level allergen sensitization and the respiratory outcomes such as wheezing or asthma. Two more studies investigating the association of allergen-specific IgE with asthma in adult patients both report that specific IgE is the most efficient predictor for asthma symptoms (5,6). The heterogeneity of these

results emphasize that asthma is a multifactorial disorder, which is still not fully understood. Even the maternal nutrition during pregnancy has been described to affect allergy development in children. While vitamin D and E as well as zinc rich food have been reported to be protective against childhood wheeze its effects are inconclusive for the later development of asthma (7).

1.2 Food Allergy

The number of physician consultations, hospitalizations and emergency department visits due to food allergies are continuously rising and add up to a remarkable economic burden for our health care systems (8,9). It is well recognized that food allergies have become a major public health issue (10). A study examining different regions of Europe has found that the overall prevalence of IgE sensitization to food allergens lies in the range of 7 - 24% (11). Generally, animal-derived foods, such as milk, egg and fish, showed weaker sensitization responses than plant-derived allergens. Interestingly, the authors described that IgE sensitization to food extracts correlated well with IgE sensitization to pollen allergens. This is explained by the observation that IgE against plant-based food allergens may cross-react with certain pollen-derived allergens. Local or systemic responses to cross-reactive airborne allergens might therefore be initiated upon first-time ingestion of a particular food. Along these lines, new cross-reactive food allergies are expected to emerge due to the increasing prevalence of pollen allergies (12).

Food allergies are often observed in early childhood. The finding that children can mount allergic responses to food which they have never been exposed before raised the question whether certain allergens might be transferred by breastmilk feeding. Indeed it has been demonstrated that major food allergens are present in breastmilk (10). However, it is still a matter of debate whether these allergens may induce tolerance or if they might promote sensitization in children (13). Recent studies in mouse models have revealed that human milk oligosaccharides (HMO) such as 2'-fucosyllactose and 6'-sialyllactose feature immune-modulatory characteristics in a mouse model of food allergy (14). Daily oral exposure of ovalbumin sensitized mice to HMO attenuated food allergy symptoms such as diarrhea and hypothermia. These effects were associated with the induction of IL-10 expressing regulatory T-cells and the authors additionally showed direct inhibition of mast cell degranulation through HMO *in vitro*. Based on these studies it is still controversial whether breastmilk feeding has beneficial effects on the development of food allergies.

1.3 Skin Allergies

Allergic skin diseases such as atopic dermatitis, urticaria and allergic contact dermatitis are heterogeneous conditions. They are often hard to control and have a significant impact on quality-of-life in affected individuals.

1.3.1 Atopic Dermatitis

Atopic dermatitis (AD) is an inflammatory disease of the skin, which is characterized by an impaired skin barrier function (15). Defective epithelial barriers (e.g. filaggrin mutations) have been reported to facilitate the entry of allergens and microbes into the body promoting inflammatory responses(16-18). The frequently observed progression from childhood AD to allergic rhinitis or asthma in later life is

referred to as the atopic march and has been linking AD to IgE sensitization against environmental allergens (19). Even though the etiology of AD is not yet completely understood most studies observed increased numbers of basophils and mast cells in skin lesions of AD patients (15). Interestingly, the reduction of skin inflammation through the use of Cyclosporine A, an immunosuppressive drug, has been reported to be accompanied by decreased expression of autoreactive IgE antibodies (20). On the other hand, loss of function mutations in the dedicator of cytokinesis 8 (DOCK8) gene have been described to induce hyper IgE syndromes (HIES). HIES show clinical overlaps to AD regarding eczema, eosinophilia, and increased serum IgE levels. A study comparing AD and DOCK8-HIES patients came to the conclusion that IgE sensitization patterns to aero- and food allergens considerably differ between the two patient groups (19). While AD patients showed higher levels of allergen-specific IgE to aeroallergens, food allergen-specific IgE was higher in DOCK8-HIES patients. Another study emphasized that there are additional parameters besides allergen-specific IgE that are associated with AD (21). The authors observed that HDM-allergic patients, which suffer from eczema, have significantly reduced levels of allergen-specific IgA₂ antibodies in serum and saliva. They report that the presence of AD directly correlates with decreased expression levels of systemic allergen-specific IgA₂. However, how and whether IgA₂ may protect against AD remains to be investigated.

1.3.2 Urticaria

Urticaria is characterized through wheal and flare reactions in the skin that are primarily induced by degranulation of local mast cells and often accompanied by angioedema (16). Depending on the symptom duration urticaria is divided into an acute (a few days) or chronic form (> 6 weeks). Based on estimations of the World Allergy Organization the life-time prevalence for acute urticaria is roughly 20% (22). Mast cell degranulation can either be induced by heat, cold, sunlight, water or pressure, known as chronic inducible urticaria or occurs in the absence of a specific stimulus, known as chronic spontaneous urticaria (CSU) (23). Interestingly, less than 1% of CSU patients have allergen-specific IgE and less than 30% have mast cell activating IgG autoantibodies against IgE or its high affinity receptor FcεRI. However, in many patients self-reactive IgE against thyroperoxidase and other autoantigens have been detected. CSU has a moderate prevalence of 0.5 – 1 % in the European population but usually persists for several years (24). Similar to many allergic skin disorders CSU has a tremendous impact on a patient's quality-of-life. Many patients have been described to develop mental problems such as anxiety, depression and somatoform disorders as a result of the wearing symptoms (24). Additionally, it has been observed that CSU patients have a significantly higher risk of internal parasite infection (PI) compared to healthy subjects (25). The authors of this study emphasize that PI might represent an underlying cause of CSU – at least in those cases where treatment of parasitosis leads to remission of CSU symptoms.

1.3.3 Allergic Contact Dermatitis

Allergic contact dermatitis (ACD), an eczematous disease of the skin, is a frequent form of delayed-type hypersensitivity affecting 15-20% of the human population (26). Despite positive associations between AD and contact sensitization certain studies have paradoxically found that AD patients have a reduced risk to develop contact sensitization (27). Similar to AD, ACD patients are positively associated with filaggrin gene mutations, which are found in about 10% of the population in northern

Europe. Individuals with filaggrin mutations are hypothesized to have an increased tendency to be sensitive to nickel (27). ACD along with other acute eczematous lesions of the skin are characterized by increased expression of interferon γ (28). Time-dependent expression of IL-17, as well as Th17-regulating cytokines were repeatedly reported in AD and ACD (16,28). However, it is yet not clear whether the presence of Th17 T-cells and eosinophils in skin lesions are coincidental or interdependent. Additionally, the association of contact sensitization in IgE-mediated reactions to proteins and allergens need to be further investigated (16,27). Recently 2,4-Dinitrochlorobenzene (DNCB) has been described to be implicated in the pathophysiology of ACD in an IgE-independent manner (29). The study reports that DNCB activates TRPA1, a nonselective cation channel on sensory neurons and induces cutaneous itch signals.

1.4 Allergic Rhinitis

Epidemiological studies report that approximately 10-20% of school-age children and adolescents suffer from allergic rhinitis (AR). These patients often experience reductions in their school and work performance (30). Additionally mental health problems such as attention deficit hyperactivity disorder, depression and anxiety disorders are increasingly found in patients with a history of AR (31). Moreover, AR may negatively affect psycho-motoric functions and may impair the driving ability (32). Along with other allergic disorders, AR is rather strongly associated with the synthesis of allergen-specific IgE and patients are three times more likely to develop other atopic disorders such as asthma (31,33) (3). AR symptoms have been described to be most severe at night or early in the morning. A recent study reports that this might be due to daily variations in basophil reactivity that is regulated by the cellular circadian rhythm (34).

Previous longitudinal studies investigated the association of TLR genes with AR. Twelve single nucleotide polymorphisms were found to be associated with the development of allergic diseases (35). The TLR6-TLR1 locus has been reported to play a central role in the development of allergic diseases (35,36). Further studies investigating polymorphisms in other TLR genes such as the TLR8 gene locus could not detect an association of AR and genetic variations in the TLR8 gene (37). These novel epidemiological and pathophysiological findings are diverse but might contribute to a better understanding of AR in the near future.

2. Diagnosis and Monitoring

Over the last decades, diagnostic tests for the identification and the monitoring of allergic disorders have remarkably improved (Table I). Advances in the standardization of allergen extracts and in the production of recombinant allergens have made this development possible and certainly contributed to the increased prevalence of allergic disorders due to better detection (38). Compared to other fields the diagnostic tools to identify allergic conditions are still relatively scarce. Often the procedures are time consuming and associated with the risk of adverse reactions.

2.1 *In vivo* diagnosis

The gold standard for the diagnosis of IgE-mediated allergic disorders is the examination of the patient's disease history in combination with *in vivo* provocation tests. Depending on the allergic condition and in order to demonstrate specific responses to the relevant allergens either dermal, conjunctival, oral, nasal or bronchial allergen challenges are routinely performed (39-42). Many of these tests include a post-challenge monitoring phase of two hours in order to exclude adverse events such as anaphylaxis. Subsequently, patients are discharged even though poorly predictable late-phase reactions may occur. A double-blind, placebo-controlled food challenge trial has recently reported that late-phase reactions are mild and do not require additional safety measures (43). Other reports, however, emphasize that biphasic anaphylaxis, which is defined as reappearance of symptoms after initial resolution may occur in rare cases. Food allergies in children have been shown to lead to an overproduction of uric acid, which could be used as a biomarker for disease monitoring (44).

The diagnosis of skin allergies is primarily based on an allergen prick tests (45,46). Skin provocation with the appropriate stimulus usually results in wheal and flare reactions within minutes. In severe cases systemic symptoms including dizziness, vertigo, vomiting, diarrhea, wheezing can develop (23). The only available test to screen for autoantibodies against IgE or FcεRI in skin allergies such as urticaria is the autologous serum skin test (ASST) (22,47). For disease monitoring the urticarial activity score for 7 days (UAS7) is now widely used.

In adults with asthma and/or rhinitis, determination of specific stimuli is also performed by skin prick tests. Strategies of allergen avoidance is obviously the first choice to improve quality-of-life (48). However, often this is difficult to achieve due to the mostly airborne nature of the specific stimuli in these conditions (49).

In the European Union, allergens that are used for *in vivo* diagnostic test are defined as medicinal products (50). This implies that every allergen involved in each test method requires authorization in each EU member state. This is associated with immense costs for the manufacturers of these allergens. Therefore, it has been suggested that regulations on the use of such products should be loosened. On the other hand, the lack of regulations has led to the production of unstandardized products on which physicians often have to rely (23,50,51). Preparation, extraction, protease content and storage conditions strongly affect the final potency of an allergen mixture, which has direct consequences on the outcome of the diagnostic tests (38,50). Therefore, standardizations and regulations are needed (52).

2.2 *In vitro* diagnosis

Due to the strong association of allergen-specific IgE with several allergic disorders, determination of the total as well as the specific IgE levels against various allergens is often used for diagnosis in eczema, food allergy, asthma and rhinitis (3,53-55). In practice a substantial discrepancy has been observed between skin prick test results and serum IgE measurements for the diagnosis of allergic sensitization (41,56,57). Genetic and environmental factors influencing IgE expression may partly differ from those involved in the development of the disorders (3). It has been recommended to assess method, age and type of investigated allergens when interpreting test results (56,58).

The identification of allergen-specific IgE-positive B-cells has failed in multiple studies. It is assumed that their frequency is too small to be detectable by flow cytometry. However, recently grass pollen-specific, circulating memory B-cell populations have been identified in blood samples from allergic rhinitis patients (59). The characterization and quantification of allergen-specific memory T- and B-cells might represent a useful *in vitro* assay, which requires further development and testing before it can be used as a diagnostic tool. Various biomarkers related to T-cell phenotypes have recently been suggested for the monitoring of allergic asthma (60), while blood coagulation markers might be useful to track chronic urticaria development (47).

In addition to the clinical history, provocation tests and IgE determination, basophil activation tests (BAT) can provide important information in the diagnosis and the monitoring of food, venom and drug allergies as well as chronic urticaria (61). BAT represents an alternative *in vitro* assay that circumvents stressful and potentially harmful allergen challenge procedures. However, this test requires well-trained staff and it has to be performed with fresh whole blood samples, which is logistically challenging. A reliable and standardized cell-based assay to test allergen reactivity in the serum of allergic patients is still lacking.

3. Treatments and Therapeutic Approaches

Various new drug targets have been identified in recent years and numerous biologicals are currently under investigation in clinical trials. Here we focus on established intervention strategies (Fig. 2) and provide insight into the latest findings.

3.1 Symptom alleviation

Many allergic conditions are treated by the use of symptom alleviating therapeutics. These compounds do not actively interfere with the development or the induction of allergic reactions but help to suppress the allergy-associated inflammation. Two of the most commonly used treatment options include corticosteroids (CS) and anti-histamines.

While CS are successfully used in a broad range of allergic conditions there is an estimated 5-10% of asthma patients who are resistant to this treatment. The reason for this CS insensitivity is still unclear. A recent study has reported that increased protein phosphatase 5 (PP5) expression in airway smooth muscle cells might contribute the insensitivity to CS in severe asthma (62). By knocking down PP5 expression in these cells *in vitro* using an siRNA-based approach CS sensitivity could be restored. Therefore, the authors suggest that targeting of the PP5 axis might offer a new therapeutic option for CS resistant asthma patients. In a randomized placebo-controlled phase 2b study it has recently been assessed whether the use of a TLR-9 agonist (CYT003) might help to overcome corticosteroid resistance in persistent moderate-to-severe allergic asthma patients. While CYT003 has shown promising results in the previous phase 2a proof-of-concept study it failed to induce additional benefits in the phase 2b study (63).

Since histamine has been attributed a key role in the allergic inflammation, treatment strategies have extensively focused on blocking its action. So far, two generations of histamine H₁-receptor (H₁R) antagonists have entered the market and have successfully been used to treat many allergic conditions, whereby first-generation antagonists should no longer be used due to the improved risk/benefit ratio

of second-generation compounds (64). The recent discovery of the histamine H₄ receptor (H4R) has raised the question whether blocking of H4R might additionally improve treatment efficacy of H₁-antihistamines. Indeed, independent groups have provided evidence that H4R is critically involved in the allergic response. One group showed that genetically engineered mice lacking H4R showed reduced allergic inflammation in a model of chronic atopic dermatitis (65). This anti-inflammatory effect could partially be mimicked by the use of an H4R antagonist (JNJ28307474). However, the authors only observed beneficial effects when the H4R antagonist has been applied during the sensitization and the challenge phase. The other group showed that simultaneous application of H1R (Loratadine) and H4R antagonists (JNJ7777120) has additive effects on the suppression of intestinal anaphylaxis in a peanut allergy model in mice (66). In the light of these results it is likely that H4R antagonists will enter the drug market soon.

3.2 Allergy-associated cytokines

Recently the Interest Group on Biologicals of the European Academy of Allergy and Clinical Immunology has provided a detailed review about different compounds that are currently available or in development for the treatment of allergic conditions (67). Many of the newly designed biologicals target cytokines which play an important role in the manifestation of allergies. These include Th2-promoting cytokines such as interleukin-4 (IL-4), IL-5, IL-9, IL-13, IL-31, and thymic stromal lymphopoietin (TSLP). Alternatively, receptors of these cytokines are targeted. Also drug candidates against pro-inflammatory cytokines, such as IL-1b, IL-12, IL-17A, IL-17F, IL-23, and tumor necrosis factor alpha (TNF α) are currently being evaluated for the treatment of allergic conditions. Due to the heterogeneous pathophysiology of different allergic conditions, it is hard to predict which of the tested drugs or drug candidates will be most efficient. Effective treatment might even require a combinatorial drug regimen simultaneously targeting multiple mediators. Future studies will help to design more tailored approaches in order to achieve maximal treatment benefit.

3.3 Allergen-specific immunotherapy

Allergen specific immunotherapy (SIT) is an immune-modifying therapeutic approach that is frequently used for the treatment of allergic rhinoconjunctivitis, asthma and venom hypersensitivities. Patients undergoing SIT receive repeated exposure to increasing doses of allergen extracts or recombinant allergens. On an immunological level SIT has been demonstrated to induce allergen-specific memory B-cells as well as IL-10 secreting regulatory B₁ cells (68) and allergen-specific regulatory T-cells (69). Whether SIT actually restores immunologic tolerance or if beneficial effects are based on a vaccination response against the applied allergen is currently under debate (70). However, it is well accepted that SIT-induced allergen-specific IgG antibodies are critical for a protective outcome of the treatment (71-73). Various research groups have exploited this concept and generated neutralizing antibodies and antibody fragments, which can be directly applied to patients (74). This passive immunotherapy approach has been demonstrated to inhibit allergen-induced basophil activation *ex vivo*. In addition, it has recently been shown that allergen-specific IgG antibodies can have direct effects on the desensitization of mast cells. These antibodies in complex with their cognate antigen (e.g. Fel-d1) can bind to the mast cell surface via the low affinity IgG receptor Fc γ RIIb, induce crosslinking with cell surface bound allergen-specific IgE and thereby promote IgE internalization. As a result, these cells become desensitized and show decreased

degranulation responses upon allergen challenge (75). In the light of these results investigations are ongoing to test whether vaccines against allergens could represent a suitable alternative to conventional SIT.

In the classical SIT protocol allergen preparations are applied by subcutaneous injections (SCIT). In order to reach long-term relief from allergic conditions it has been suggested that SCIT is performed at least 3-5 years. Nevertheless, there are studies questioning these long-term effects (76). Long treatment durations imply frequent visits at the medical doctor. Additionally, it has been recommended that each patient is observed for 30 minutes in the clinic after allergen injection to exclude adverse reactions. In order to facilitate the treatment procedure and to minimize associated medical costs a lot of effort has been put into the development of alternative application routes, which are safer and can be administrated by the patient on its own. There is accumulating evidence that sublingual immunotherapy (SLIT) could replace the classical SCIT regimen. A double-blind, placebo-controlled, randomized study including 484 asthmatic adults, which were treated daily for 12 months with sublingual HDM extract, reports that SLIT is well tolerated and efficiently controls disease in patients with moderate asthma (77,78). Another double-blind study investigating sublingual house dust mite immunotherapy in patients with allergic rhinitis has been conducted in Japan and has found similar results concerning safety and efficacy (79). Both studies recommend treatment with 300 index of reactivity tablets. Furthermore, a *post hoc* analysis of two randomized, double-blind, placebo-controlled trials testing sublingual timothy grass immunotherapy in patients with allergic rhinitis and asthma reported no increased frequency of treatment-related adverse events (80). Recently, a new sublingual tablet based on recombinant Bet v 1 (rBet v 1) has been development and evaluated in birch pollen allergic patients. This multicenter, double-blind, placebo-controlled study included 483 patients. The new product was well tolerated and showed a favorable safety profile. Patients receiving rBet v 1 SLIT daily for five months showed a decreased rhinoconjunctivitis symptom score relative to the placebo group (81). Overall, these studies indicate that SLIT seems to be a well-tolerated and efficient alternative to classical SCIT.

Epicutaneous allergen immunotherapy (EPIT) has recently been suggested as another desensitization approach. In this method a patch containing allergen extracts is applied onto tape-stripped skin of the patient. A study summarizing three clinical trials in which patients suffering from grass pollen rhinoconjunctivitis have been treated with EPIT has recently been presented (82). The authors described that conjunctival allergen reactivity was decreased and that allergen-specific IgG₄ responses were elevated after allergen EPIT but not placebo EPIT. Even though the efficacy and safety profile in this trials showed promising results the authors emphasized that further research is required to determine an optimal treatment regimen that balances clinical efficacy and safety. Prophylactic as well as therapeutic EPIT with rBet v 1 plus R848 (Resiquimod), a TLR7 agonist, suppressed lung inflammation upon intranasal allergen challenges through induction of a Th1 response. The authors conclude that R484 represents a promising adjuvant that might be used in allergen-specific EPIT in the near future.

In order to reduce the risk of adverse reactions through allergens used in SIT and to accelerate the treatment regimen researchers have put a considerable effort into the development of alternative allergen variants. A hypoallergic form of rBet v 1 (rBet v 1B2) consisting of a protein folding variant has been tested using EPIT in a mouse model of birch pollen allergy (83). Prophylactic application of rBet v 1B2 decreased serum levels of Bet v 1-specific IgE antibodies, reduced the number of eosinophils in the lung and lowered the concentration of Th2 cytokines in the bronchoalveolar lavage after sensitization with rBet v 1 plus alum adjuvants and intranasal challenges with birch pollen extract. Therapeutic application of rBet v 1B2 successfully suppressed the development of airway

inflammation and lung function impairment in these mice. SIT is generally carried out in two stages. An allergen up-dosing phase and a maintenance phase. To achieve the maintenance dose in a shorter timeframe medical doctors have started to use polymerized allergen extracts - known as cluster immunotherapy. Recently a randomized, double-blind, placebo-controlled, multicenter trial has been presented, in which the efficacy and safety of cluster immunotherapy has been evaluated (84). The study included 121 patients with allergic rhinoconjunctivitis from which 62 received a highly polymerized grass/rye pollen mixture using a conventional SCIT regimen and 59 patients received a placebo. The up-dosing phase was performed for one week after which the patients received a monthly maintenance dose for one year. A reduction of the total combined score, the rhinoconjunctivitis total symptom score and the total rescue medication score has been found in the group receiving cluster immunotherapy compared to the placebo treated control group. No severe adverse reactions have been observed. The authors conclude that the use of polymerized pollen mixtures for the treatment of grass pollen allergies is safe and efficient.

Since there is a high degree of clinical and methodological heterogeneity among the endpoints in clinical studies using SIT, an EAACI position paper has recently been published outlining standardized recommendations for clinical outcome measures (85). The task force of authors suggests a homogeneous combined symptom and medication score as the primary endpoint for future SIT trials. A second EAACI position paper has been published concerning clinical contradictions to the use of SIT (86). The task force has performed an extended literature search and provides general recommendations for various medical conditions. However, the authors emphasize that the administration of SIT should ultimately be based on individual evaluation of the patient's medical condition and a thorough risk/benefit assessment.

3.4 Anti-IgE therapy

As outlined above, allergen-specific IgE plays a key role in the development and the initiation of allergic responses in various disease conditions. Thus, it is clear that IgE represents an interesting drug target for intervention strategies. Anti-IgE antibodies blocking the interaction of soluble IgE with its high affinity receptor FcεRI on allergic effector cells have been developed by various companies and follow up antibodies are currently under investigation in clinical trials (67). The widely used anti-IgE antibody, Omalizumab (Xolair®), has been approved by the FDA in 2003 for the treatment of moderate-to-severe allergic asthma. A systematic review including 4117 unique patients from 32 countries has recently emphasized signal improvements across the full objective and subjective burden of illness chain of severe allergic asthma (87). These benefits extend at least up to 2–4 years and the majority of Omalizumab-treated patients benefit even longer. Various effect of Omalizumab treatment on allergic effector cells such as desensitization and FcεRIα down-regulation have previously been described. However, the role of basophils in allergic asthma still remains an active area of investigation. A study examining basophil populations in children before and during Omalizumab treatment has demonstrated a reduction in circulating basophil numbers (88). These findings suggest that basophils might play an important role in the asthma pathology and provide a mechanistic link between anti-IgE therapy and improvement of disease parameters.

In the meantime, efficacy of Omalizumab has been proven in various other IgE-related disorders. In 2012 Omalizumab has additionally been approved for the treatment of chronic spontaneous urticaria (CSU). Recently the results of a phase III, randomized, double-blind multi-center study, called X-ACT, have been published, in which the efficacy of Omalizumab treatment in H₁-antihistamine

resistant CSU patients has been evaluated (89). Patients received 300 mg Omalizumab injections every four weeks over a total of 24 weeks. Omalizumab treatment led to improvements in quality-of-life. The results of this study suggest that Omalizumab represents a suitable treatment option for moderate-to-severe CSU patients, which are resistant to high doses of antihistamines.

A recent small-scale study further assessed the efficacy of Omalizumab treatment in moderate-to-severe atopic dermatitis patients (90). Twenty patients were included in this open-label trial. Patients received 150 mg Omalizumab in 2-week intervals for a total of 28 weeks. As a read out SCORAD (SCORing Atopic Dermatitis) has been assessed. The subgroup of patients with wildtype filaggrin status responded with a reduction in SCORAD, while patients with filaggrin mutations did not benefit from the treatment. The authors conclude that Omalizumab treatment can be successfully used in patients without primary skin barrier deficiency.

4. Concluding remarks

Even though IgE is an important key player in allergic reactions researchers are increasingly realizing that also IgE-independent components contribute to disease manifestation and progression. The multifactorial etiology reflects the complexity of allergies and the heterogeneous clinical manifestations underline the broad diversity of these diseases. The variety in pathophysiology of allergic disorders poses major challenges for the development of diagnostic tests. While *in vivo* testing is very time-consuming and associated with the risk of adverse events, *in vitro* measurements do not always correspond to the clinical picture. This lack of correlation indicates that there is an urgent need for better *ex vivo* diagnostics helping to identify disease-associated biomarkers and to choose appropriate therapeutic intervention strategies. Several promising treatment approaches interfering at different stages of the allergic cascade are currently under evaluation (Fig. 2). Considering the multifactorial pathogenesis of allergic diseases combinatorial approaches such as targeting of multiple disease-relevant factors might be an interesting strategy for future directions. Ultimately, we hope that the increasing knowledge about basic mechanisms underlying allergic disorders will soon translate into more efficient treatment options for patients.

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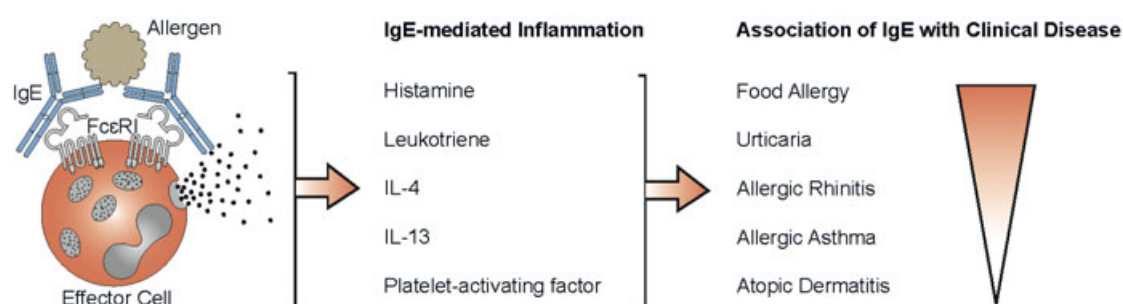


Fig. 1 IgE-mediated inflammation in allergic disorders. IgE-dependent release of pro-inflammatory mediators from allergic effector cells such as basophils and mast cells contributes to local and systemic inflammation. While the clinical manifestation of food allergies and urticaria is strongly IgE-dependent, the association with IgE is less obvious for other allergic conditions such as allergic asthma and atopic dermatitis.

Table I. Overview of diagnosis and monitoring approaches used for allergic disorders.

Allergic Disease	Diagnosis and Monitoring	References
Allergic Asthma	Specific IgE (sIgE)	(5,55,60)
	IL-5 expression	(60)
	IL-17A expression	(60)
	IL-25 expression	(60)
	Sputum eosinophil, neutrophil count	(60)
	Airway hyper-reactivity (AHR)	(39)
Food Allergy	Clinical history	(42,57)
	Specific IgE (sIgE)	(12,41,42,57)
	Skin prick test (SPT)	(12,42,46,57)
	BAT (Basophil activation test)	(42,61)
	Food provocation test	(12,39)
Atopic Dermatitis	Specific and total IgE	(16,41)
Chronic Urticaria	BAT (Basophil activation test)	(22,47,61)
	Provocation test (drug, food and physical test)	(22)
	Autoantibody against IgE and/orFcεRI (ASST)	(22,47)
	UAS7 (urticaria activity score)	(22)
	D-dimer level	(47)
Chronic inducible Urticaria	Skin prick test (SPT)	(22)
Cold Urticaria	Cold source	(23)
Heat Urticaria	Heat source	(23)
Delayed Pressure Urticaria	Weight pressure	(23)
Solar Urticaria	UVA , UVB and visible light	(23)
Allergic Contact Dermatitis	Skin patch test (PT)	(26)
	Lymphocyte proliferation test (LPT)	(26)
Allergic Rhinitis	Clinical history	(39)
	Specific IgE (sIgE)	(39,55)
	Skin prick test (SPT)	(39)

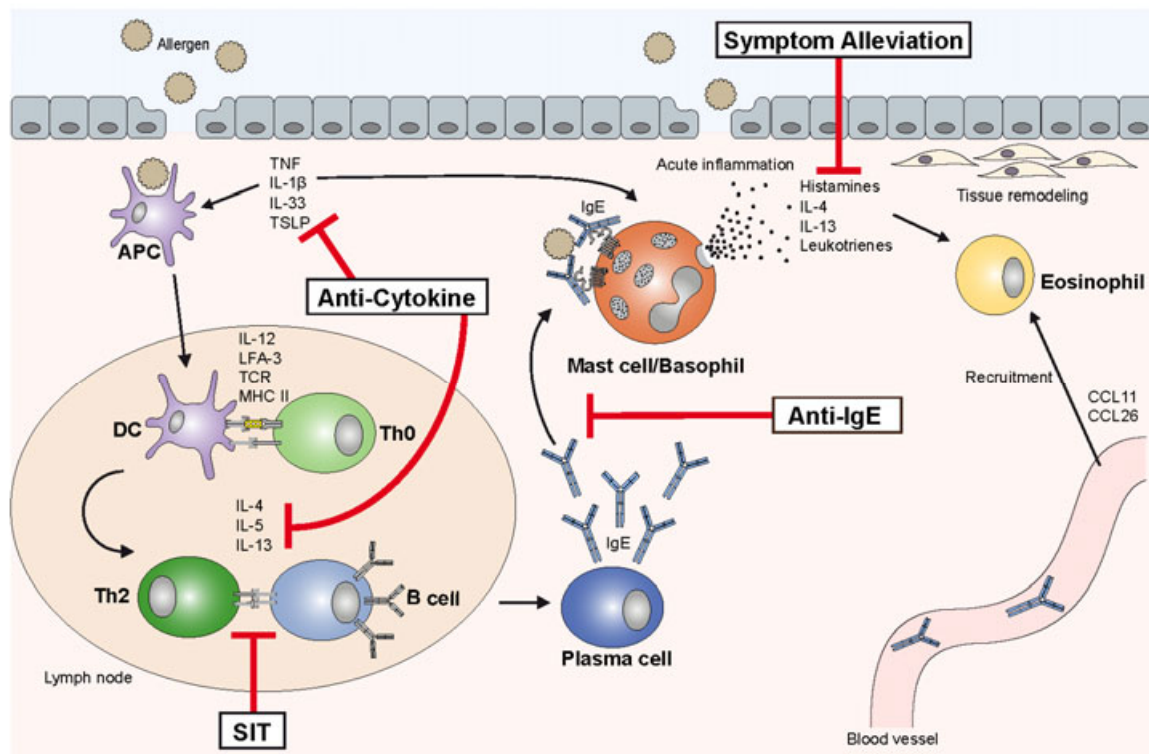


Fig. 2 Overview of current intervention strategies for the treatment of allergic disorders. Often symptom alleviation is successfully achieved using corticosteroids or anti-histamines to suppress allergy-associated inflammation. Many emerging and newly developed biologicals target cytokines and receptors, which are directly involved in the development and manifestation of allergies. Specific immunotherapy (SIT) is an immunomodulatory approach with the aim to skew Th2 responses towards Th1 immunity. Based on the key role of IgE in allergic disorders, anti-IgE antibodies blocking soluble IgE are used to prevent allergic effector cell activation.