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Immunotherapy: State-of-the-art review of therapies and theratypes

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Through its disease-modifying potential, immunotherapy is the keystone to curing allergic diseases. Allergen immunotherapy, applied for more than a century, is currently supported by novel modalities such as mAb-based therapies or small molecules targeting the key nodes of the allergic inflammation network. In this review, a summary of the most significant advances in immunotherapy is presented, addressing not only novel approaches to stratifying patients but also major controlled clinical trials and real-world evidence that strengthen the role of immunotherapy in the treatment of allergies. (*J Allergy Clin Immunol* 2022;■■■:■■■-■■■.)

Key words: Allergen, biomarkers, biologicals, endotypes, immunotherapy, theratype

Immunotherapy is defined as the treatment of disease by activating, suppressing, or modulating the innate and adaptive immune responses. Acting on immune and effector cells, immunotherapy can exert an immediate effect. However, the most valuable feature of this drug is its long-term efficacy, which persists after discontinuation. This is referred to as the “disease moderating” effect. Allergen immunotherapy (AIT) has been used for more than a century, and its short- and long-term efficacy has been well-established. Novel preparations and methods are

Abbreviations used

AD:	Atopic dermatitis
AIT:	Allergen immunotherapy
AR:	Allergic rhinitis
CAR:	Chimeric antigen receptor
CRISPR:	Clustered regularly interspaced short palindromic repeats
cT _{FH} :	Circulating T _{FH}
DC:	Dendritic cell
EAR:	Early asthmatic reaction
HDM:	House dust mite
HETE:	Hydroxyeicosatetraenoic acid
ILC:	Innate lymphoid cell
LAR:	Late asthmatic reaction
miRNA:	Micro RNA
OIT:	Oral immunotherapy
RWE:	Real-world evidence
SCIT:	Subcutaneous immunotherapy
SLIT:	Sublingual immunotherapy
T2:	Type 2
T _{FH} :	T follicular helper
T _{FR} :	T follicular regulatory
Treg:	Regulatory T

being developed to improve its efficacy, safety, and cost-effectiveness. As a consequence of a better understanding of allergic inflammation pathogenic pathways, the therapeutic armamentarium has been enriched with targeted interventions using mAbs or small molecules targeting the type 2 (T2) immune response key molecules and the epithelial-derived cytokines.

This review highlights the advances in immunotherapy, including AIT, biological treatments, and small molecules. We discuss the practical implications of using phenotyping and endotyping in facilitating the stratification of patients into responding and nonresponding populations and defining the theratypes. The pivotal clinical trials and the real-world evidence (RWE) are critically appraised. The role of immunotherapy in allergy prevention and its future perspectives are also reported.

PHENOTYPING AND ENDOTYPING: IMPLICATIONS FOR CLINICAL PRACTICE

Key advances in the understanding of AIT mechanisms and biomarkers are presented in [Table 1](#) and [Figs 1](#) and [2](#).

There is increasing evidence that T follicular helper (T_{FH}) cells (especially T_{FH}2 and T_{FH}13), rather than T2 lymphocytes (T_H2), significantly influence the production of IgE. T follicular regulatory (T_{FR}) cells inhibit their action. In patients with allergic diseases, upregulation of T_{FH} cells and a reduced frequency of T_{FR} cells have been observed. AIT may reestablish this balance toward the ratio of healthy subjects.¹ Circulating C-X-C chemokine receptor type 5⁺ programmed death receptor 1⁺ T follicular

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TABLE I. Key advances in AIT

AIT mechanism		Reference
T _{FH} and T _{FR} cells	T _{FH} increased and T _{FR} decreased in allergic patients; AIT may rebalance this ratio	1
CXCR5 ⁺ PD-1 ⁺ cT _{FH} , secreting IL-4 and IL-21	Increased in allergic patients, decreased by SCIT and SLIT	2
cT _{FH} secreting IL-10	Observed in SLIT and SCIT and correlated with the clinical response	2
Anti-inflammatory monocytes, CD25 ⁺ ILCs, plasmacytoid DCs, CD141 ⁺ myeloid DCs	Increased under AIT	3
Naive and memory $\gamma\delta$ Treg cells	Reached a similar level to healthy controls after POIT and might be early marker of desensitization	4
Local and systemic IgA production	Increased in SLIT vs SCIT and correlated with the clinical response	5
The Notch signaling pathway IL-10 ⁺ CD4 ⁺ cells, IL-4 ⁺ and IL-10 ⁺ T _H 2 cells, and myeloid-derived suppression cells	Linked to sustained unresponsiveness in OIT (murine model)	6
Skin DCs: Langerhans cells, conventional type 1 and 2 DCs (cDC1 and cDC2)	Acquired varied phenotypic and functional specializations under EPIT (murine model)	7
Allergoid-mannan conjugates as adjuvants	Reprogramed monocytes into stable tolerogenic DCs	8
Biomarkers		Reference
IL-10 ⁺ CTLA4 ⁺ ILCs	Increased in responders after AIT	9,10
CD38 ⁺ B cells	Poor therapeutic effect of AIT	11
Allergen-specific IL-4 ⁺ and IL-13 ⁺ CD4 ⁺ cells (T2 cells) at baseline	Threshold of response to AIT	12
IgA ₁ in nasal fluid	Increased in SLIT	5
IgG ₄ in nasal fluid	Increased in SCIT	13
Serum periostin	Increased in SLIT	14
Basophil sensitivity	Decreased in SCIT	15
Metabolic biomarkers: 12(S)-HETE and 15(S)-HETE	Significantly higher in the asthma group than in healthy individuals. Their levels increased in the first year of SCIT treatment and then decreased from years 1-3, significantly lower after 3 y of therapy than baseline levels	16
Metabolic biomarkers: 5(S)-HETE, 8(S)-HETE, 11(S)-HETE, 15(S)-HETE, and 11-hydro TXB2	Significant difference after ~1 y of treatment, and the changes were correlated with the magnitude of RQLQ improvement	17
Bronchial allergen challenge	Significant effect of SCIT (similar to ICS) on the EAR to mite, cat, birch, and grass pollens in children and adults; patients who developed a dual response (EAR and LAR) with high eosinophilic inflammation are more likely to respond to AIT	

EPIT, Epicutaneous immunotherapy; ICS, inhaled glucocorticosteroid; PD-1, programmed death receptor 1; POIT, peanut OIT; RQLQ, rhinoconjunctivitis quality of life questionnaire; TXB2, thromboxane B2; $\gamma\delta$ Treg, gamma delta regulatory T.

helper (cT_{FH}) cells that secrete IL-4 and IL-21 are distinct from T_H and T_H2A cells and promote B-cell switching into IgE production. These cells were shown to be more frequent in the grass-pollen-allergic patients compared with healthy controls. Increased IL-4 and IL-21 production was observed in the nasal secretion after nasal challenge in the grass-pollen-allergic group compared with patients receiving subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). SLIT and SCIT patients significantly increased cT_{FH} IL-10⁺ and T_{FR} cells. A shift in the chromatin landscape was observed in cT_{FH} and T_{FR} cells in both SLIT and SCIT patients.²

In a murine model of epicutaneous immunotherapy, skin dendritic cells (DCs) such as Langerhans cells and conventional type 1 DC and type 2 DC subset cells acquired varied phenotypic and functional specializations. Langerhans cells lost their ability to stimulate CD4⁺ T-effector cells but acquired the skill to stimulate regulatory T (Treg) cells; in contrast, conventional type 1 DCs lost the capacity to prime CD4⁺ T-effector cells, whereas type 2 conventional DC gained the capacity to induce T_H1/T_H17 responses.⁷ The allergoid-mannan conjugates are a new product for AIT that generate Treg forkhead box P3. The monocytes could be reprogrammed into stable tolerogenic DCs that activated Treg cells, secreted IL-10, and enhanced the

expression of anti-inflammatory factors such as micro RNA (miRNA)-146a/b, enhanced mitochondrial activity, or boosted the expression of programmed death-ligand 1 (PD-L1), indoleamine 2,3-dioxygenase, and suppressor of cytokine signaling 1 regulatory molecules.⁸

AIT can modify the phenotype of the innate immune cells in such a way that the repertoire resembles healthy individuals. AIT switched monocytes from the proinflammatory to the anti-inflammatory phenotype, augmented the frequency of CD25⁺ innate lymphoid cells (ILCs), plasmacytoid dendritic cells, and CD141⁺ myeloid dendritic cells, and decreased type 2 ILCs and type 3 ILCs.³

Gamma delta regulatory T ($\gamma\delta$ Treg) cells may contribute to the tolerogenic effect of AIT. After 24 weeks of peanut oral immunotherapy (OIT), naive and memory $\gamma\delta$ Treg cells stabilized to a similar level as in healthy controls. Transcriptomic studies in memory $\gamma\delta$ Treg cells showed that anti-inflammatory genes were upregulated and proinflammatory genes were downregulated.⁴ These cells might be an early marker of desensitization in subjects undergoing peanut OIT.

A detailed longitudinal assessment comparing nasal and systemic antibody responses during SLIT and SCIT with grass pollen showed increased local and systemic IgA₁/IgA₂ in SLIT

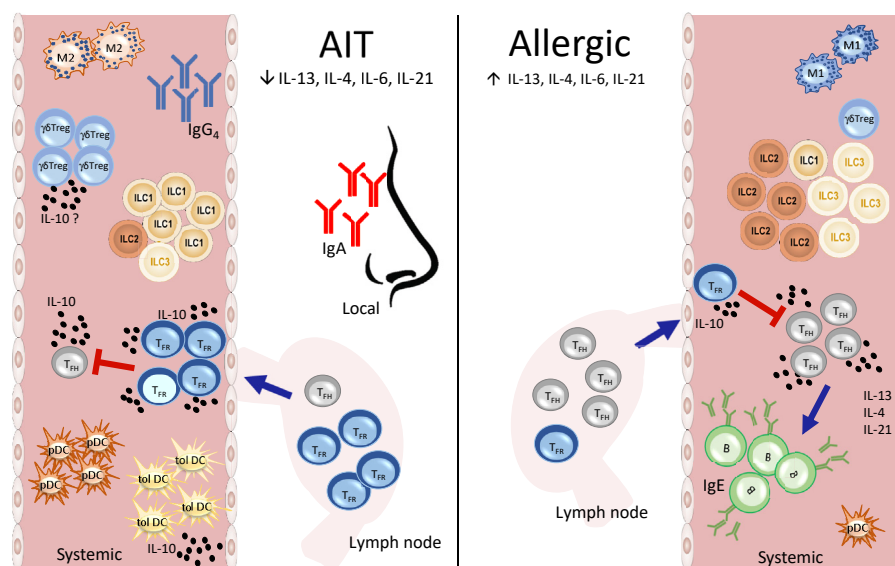


FIG 1. New proposed mechanism for AIT. T_H cells play a central role in controlling T2 inflammation and IgE production. T_{FR} cells restrict T_H cells. Circulating T_H cells release IL-10 after SLIT and SCIT and IL-4/IL-21 after grass pollen stimulation. An increase in T_H cells and switching toward the T_H2 IL-13 phenotype, together with a deficit in T_{FR} cells, have been reported in patients with allergic diseases. AIT may reestablish this imbalance. The frequency of ILC2, ILC3, and pDC decreased, whereas ILC1 cells increased during AIT, bringing their ratio closer to that in healthy individuals. A proinflammatory circulating monocyte shifts its phenotype toward an anti-inflammatory cell after the first year of AIT. Memory and naive $\gamma\delta$ Treg cells contribute to the tolerogenic effect of peanut OIT and may be an early marker of desensitization. Grass pollen-specific IgA antibodies are upregulated in serum and nasal fluid in SLIT patients as compared with IgG4 in serum in SCIT. Under the influence of the allergoid-mannan conjugates, monocytes from healthy and allergic individuals can be reprogrammed into tolerogenic DC cells. B, Lymphocytes B cell; ILC1/2/3, type 1/2/3 ILC; M1/M2, proinflammatory (nonclassical)/anti-inflammatory (intermediate) monocytes; pDC, plasmacytoid DC; T, lymphocyte cell; tol DC, tolerogenic DC; $\gamma\delta$ Treg, naive and memory gamma delta regulatory T.

compared with SCIT. At the same time, serum IgG induction was higher with SCIT.⁵

A high-content allergen peptide microarray assessing the so-called linear epitopes recognized by IgE, IgG, and IgG4 was used to evaluate the antibody response after SCIT with grass and birch pollen.¹⁸ After 1 year of AIT and beyond, the immunized cohort displayed substantial levels of allergen peptide reactivity, showing that AIT leads to linear epitope-recognizing humoral immunity that is not a prominent part of natural sensitization. The pattern of epitopes detected was stable over time in a given individual, suggesting that antibody-producing clones established early during the AIT response retain a dominant position over time.

Notch signaling contributed to the development of IL-10⁺ CD4⁺ cells, IL-4⁺, and IL-10⁺ T_H2 cells, and myeloid-derived suppression cells during OIT. These cells collaborated in inducing sustained unresponsiveness to food allergens. Inhibition of Notch signaling impacted achieving sustained unresponsiveness but did not influence the desensitization of mice undergoing OIT.⁶

THERATYPES

The concept of a theratype was introduced to describe the potential therapy responders and nonresponders on the basis of compilation of pathophysiological mechanisms explaining disease expression and response to therapy in different groups of patients.¹⁹ The possible relevance of biomarkers associated with theratypes in AIT or biologicals is revised in this section.

In AIT

For AIT, several new biomarkers for the stratification of patients and early assessment of its efficacy (early stopping rule) were reported. A recently identified ILC subset that produced IL-10 and expressed cytotoxic T-lymphocyte-associated protein 4 was shown to increase after 24 months of AIT in patients with allergic rhinitis (AR) triggered by house dust mite (HDM). The increase in IL-10⁺ cytotoxic T-lymphocyte-associated protein 4⁺ ILCs correlated with the combined symptom-medication score.⁹ The underpinning mechanisms were associated with the modification of the retinol metabolic pathway, cytokine-cytokine receptor interaction, and Janus kinase-signal transducer and activator of transcription protein signaling pathways in the ILCs.¹⁰ Another study showed that CD38⁺ expression in B cells was associated with the poor therapeutic effects of AIT in patients with AR. By releasing IL-6 on exposure to specific antigens, CD38⁺ B cells converted Treg cells into T_H17 cells. Peripheral CD38⁺ B-cell frequency was negatively correlated with CD4⁺CD25⁺CD127⁺ Treg-cell and T_{FR} -cell frequencies. Coadministration of anti-CD38 mAb significantly potentiated AIT results and increased the induction of Treg cells.¹¹

Two AIT trials assessed the relationship of the food allergen-specific T-cell response to clinical phenotypes, including response to AIT. At baseline, T2 cells, but not chemokine receptor protein 6⁺ cells, were predictive of peanut and baked egg tolerance. High egg-specific T2-cell frequency was the immune feature most predictive of OIT failure.¹²

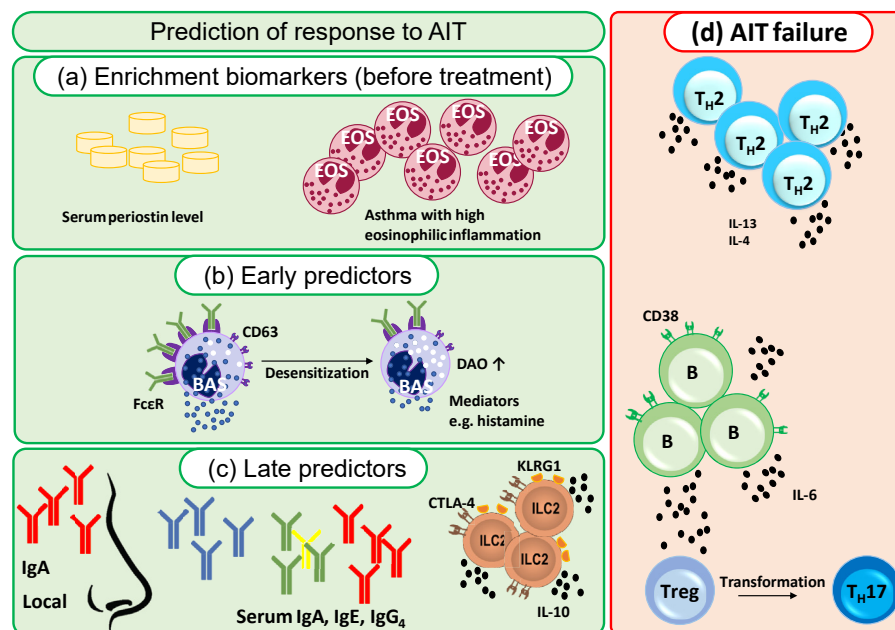


FIG 2. New biomarkers for the stratification of patients and for assessment of AIT efficacy. Prediction of AIT response: (a) enrichment biomarkers (before treatment): High serum periostin levels are associated with an effective response to SLIT. AIT responders demonstrate a high eosinophilic response after exposure to the allergen. (b) Early predictors of response: A decrease in basophil sensitivity after 3 weeks of treatment predicts long-term improvement in seasonal symptoms and medication scores during 3 years of AIT. (c) Late predictors of response: Patients with TNSS reduction from baseline to year 2 show increased serum and local IgA to grass extract and more serum IgG₄ and IgE to grass components from baseline to year 1. Induction of IL-10⁺KLRG1⁺CTLA-4⁺ILCs is associated with the improvement in symptoms during AIT in responders. The restoration of the IL-10 production by ILC2 parallel the clinical benefit of grass SLIT. (d) AIT failure: CD38⁺ B release IL-6 and convert Treg cells into TH17 cells, which negatively correlated with AIT efficacy. A high frequency of specific type 2 cells (CD4⁺ T cells coexpress IL-4 and IL-13) predicted treatment failure with egg OIT. B, Lymphocytes B cell; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; DAO, diamine oxidase; EOS, eosinophil; ILC2, type 2 innate lymphoid cell; KLRG1, killer cell lectin-like receptor G1; TNSS, total nasal symptom score.

The levels of IgA₁ in nasal fluid correlated with SLIT's suppression of nasal symptoms during the nasal allergen challenge. The addition of grass-pollen-specific serum IgA, IgE, and IgG₄ to various other parameters as part of an exploratory cluster analysis of the changes from baseline to year 1 enhanced the ability to identify patients not responding to treatment at year 2 of AIT.⁵

High serum periostin levels were associated with an effective response to SLIT. The magnitude of rhinoconjunctivitis quality of life questionnaire improvement directly correlated with the level of serum periostin.¹³

Basophil response to allergens is a valuable tool for monitoring the effects of AIT and of other immunomodulatory treatments, such as anti-IgE. A grass AIT study in adults with AR SCIT led to a 447-fold decrease in basophil sensitivity during the first treatment year. This remained 100-fold lower than baseline during the 3-year-treatment periods and 10-fold lower during the follow-up year. The decrease in basophil sensitivity after 3 weeks of SCIT predicted long-term improvement in seasonal combined symptom-medication score during 3 years of treatment.¹⁴ A new functional allergy screening assay with remarkable diagnostic potential uses passive sensitization of human high-affinity IgE receptor transgenic and conditional homeobox B8-immortalized progenitor-derived mouse mast cells with patient serum.²⁰ The progenitor cells have a high replicative rate and a near-unlimited renewal potential, allowing on-demand *in vitro*

differentiation of large numbers of functional homeobox B8 mast cells within a few days. This test might assess whether and when patients respond to AIT through longitudinal tracking of serum reactivity.

Metabolic biomarkers are currently being tested for monitoring AIT response in allergic asthma or in AR. Targeted metabolomic analysis of sera of children with allergic asthma receiving SCIT revealed that levels of eicosanoids, particularly 12(S)-hydroxy-eicosatetraenoic acid (HETE) and 15(S)-HETE, were significantly higher as compared with those in healthy individuals.¹⁵ Their levels increased in the first year of SCIT treatment and then decreased from years 1 to 3, significantly lower after 3 years of treatment than baseline. Another study with HDM SCIT in AR 5(S)-HETE, 8(S)-HETE, 11(S)-HETE, 15(S)-HETE, and 11-hydro thromboxane B2 showed significant differences after approximately 1 year of treatment, and the changes were correlated with the magnitude of rhinoconjunctivitis quality of life questionnaire improvement.¹⁶

Another interesting biomarker for AIT in allergic asthma is the bronchial allergen challenge. As for other asthma controllers, an effect of AIT on the early asthmatic reaction (EAR) and the late asthmatic reaction (LAR) should be demonstrated. SCIT appears to significantly affect the EAR to mite, cat, birch, and grass pollens in children and adults. Dual responses (EAR and LAR) are less studied. However, a reduced response to mite, birch, and

TABLE II. Key advances in biologicals theratypes

Biological/marker	Observed outcome	Reference
Serological degradation marker of the inflammation-protective collagen 4 (C4Ma3)	Elevated in severe, exacerbating asthma predicts response to omalizumab	21
Benralizumab	Unresponsiveness in severe asthma with neutrophil-related gene expressions	22
Mepolizumab	Ventilation/perfusion single photon emission computed tomography as a tool for assessing response to biological treatment	23
Dupilumab	Monitoring of therapeutic responses in AD by molecular profiling of tape-strips	24
	In AD nonresponders display low CXCR5 ⁺ and high CXCR5 ⁺ T _{FH} cells compared with responders	25
Omalizumab	Basophil histamine release as a predictor for responsiveness in CSU	26
	Basopenia was associated with autoantibodies to FcεRI in CSU	27
	Basophil miRNA as a predictor for patients with CSU with omalizumab intervention	28
	Allergen-specific/total IgE as a predictor for patients at greater risk of food dosing reactions under OIT	29

CSU, Chronic spontaneous urticaria; CXCR5, C-X-C chemokine receptor type 5; FcεRI, receptor for the Fc region of IgE.

grass was reported. The magnitude of the effect was close to those of other controllers (eg, inhaled corticosteroids). Patients who develop a dual response (EAR and LAR) with high eosinophilic inflammation are more likely to respond to AIT.¹⁷

In biologicals

Guiding treatment decisions (choice of the biological, efficacy assessment, duration of administration, stopping and switching rules) for patients receiving biologicals for severe uncontrolled asthma and allergic diseases is still a blurry field due to the lack of validated predictive biomarkers. However, in recent years, the body of evidence has been growing (Table II).

In severe asthma, response to dupilumab (anti-IL-4 and IL-13) seems not to be impacted by patient demographic or disease characteristics at baseline.³⁰ The serological degradation marker of the inflammation-protective collagen 4 (C4Ma3) was reported to be associated with severe, exacerbating allergic asthma phenotype and, measured at baseline, predicted the success of the anti-IgE therapy in patients with allergic, uncontrolled asthma with a diagnostic odds ratio of 31.5.²¹ Gene expression patterns in response to benralizumab were evaluated to predict clinical responsiveness to the biological. Nonresponsiveness to benralizumab was associated with neutrophil-related gene expressions.²² Newer imaging methods were also tested for evaluating response to biologicals in asthma. Ventilation/perfusion single photon emission computed tomography proved to be an objective method to assess responsiveness to mepolizumab.²³

The transcriptomic profile was assessed by tape strips in patients with moderate to severe atopic dermatitis (AD) treated with dupilumab. The gene expression change was observed in immune and barrier biomarkers correlated with clinical disease improvements.²⁴ The proportions of T_H1, T_H2, T_H17, T_H1/T_H17, T_{FH}1, T_{FH}2, T_{FH}17, and T_{FH}1/T_{FH}17 were evaluated in the peripheral blood of patients with chronic AD before and after dupilumab. Low responders displayed significantly lower levels of C-X-C chemokine receptor type 5⁺ total T_{FH} cells than did strong and intermediate responders.²⁵ This difference was also identified for T_{FH}1 and T_{FH}2 cells. Conversely, low responders displayed higher levels of C-X-C chemokine receptor type 5⁺ cells at more than 12 months of therapy than did high and intermediate

responders. T_{FH}17 and T_{FH}1/T_{FH}17 cell percentages were not significantly different between the 2 groups.

Patients with chronic spontaneous urticaria who were not basopenic demonstrated the most rapid and complete symptom improvement following treatment with omalizumab (anti-IgE mAb). The basophil functional phenotype, as determined by histamine release, was predictive of responsiveness to omalizumab. Changes in basophil IgE-based histamine release, surface IgE, or high-affinity receptor for the Fc region of IgE had no predictive value.²⁶ Changes in basophil function in relationship to autoantibodies in serum were also evaluated. Basopenia was highly associated with the presence of autoantibodies in unoccupied receptor for the Fc region of IgE. In this group, basophil numbers did not change during treatment, and there were no changes in cellular spleen tyrosine kinase (SYK) expression or histamine release during treatment.²⁷ Two other studies evaluated the role of miRNAs as predictors of response to omalizumab. They reported a unique set of differentially expressed extracellular vesicle miRNAs in patients with refractory chronic spontaneous urticaria, predicting complete response to omalizumab, thus suggesting that the basophil miRNA expression profiles identified (miR-4664-3p, miR-1200, and miR-1236-3p) could serve as a diagnostic panel to guide physicians in selecting patients with chronic spontaneous urticaria for omalizumab intervention.²⁸

Patients treated with omalizumab-enabled OIT have been evaluated for determinants of omalizumab dose-related efficacy. Patients received omalizumab for at least 2 months before an initial food escalation with a mix of up to 6 allergens. Continued food dose tolerance with omalizumab weaning was also documented. The fraction of allergen-specific/total IgE proved helpful in predicting patients at a greater risk of food dosing reactions subsequent to weaning.²⁹

CLINICAL TRIALS

Allergen immunotherapy

Significant progress was achieved in the treatment of peanut and milk allergy, with high-quality long-duration trials focused on evaluating the efficacy and safety of the novel AIT formulations and delivery routes, together with predictors of response. In the open-label extension of the epicutaneous immunotherapy study for peanut allergy,³¹ the intervention was well tolerated, and the

TABLE III. Novel targeted approach in allergic diseases

Novel mAbs and small molecules	Observed outcome	Reference
Tezepelumab	Improvements in asthma-related outcomes independent of eosinophilic profile	51
Astegolimab	Reduce exacerbation in severe asthma independent of eosinophilic profile	52
Itepekimab	Improvements in asthma control, reduction of exacerbation in COPD	53,54
Risankizumab	Ineffectiveness in severe asthma	55
Fezakinumab	Transcriptomic signature for severe neutrophilic asthma in responders, effectiveness in AD	56,57
Inhaled JAK inhibitor	Reduced inflammatory response in mild asthma	58
Nucleic acid nanocapsule as a delivery vehicle for GATA3 DNzyme	Decreased allergic inflammation in asthma (murine model)	59

COPD, Chronic obstructive pulmonary disease; JAK, Janus kinase.

desensitization observed at week 52 persisted between weeks 52 and 130. An association of better response with younger age was noticed. The IgG₄ specific for Ara h 2 significantly increased.³² An improvement in food allergy quality of life after 2 years of epicutaneous immunotherapy in peanut-allergic pediatric patients was reported.³³ The safety of peanut allergen powder usage was confirmed for up to 2 years of OIT in children, while most allergic symptoms decreased in severity and frequency.³⁴ A novel baked milk OIT achieved desensitization in pediatric patients after 1 year of treatment, together with an increase in cow's milk IgG₄.³⁵

For AIT with inhaled allergens, long-term trials, novel formulations, and administration schemes together with a particular focus on AIT impact on comorbidities (eg, AD) or on recently described phenotypes (local AR) were reported. HDM SLIT tablets proved to be an effective and safe treatment for HDM-triggered AR in an international, double-blind, placebo-controlled, randomized phase III trial.³⁶ SLIT therapy with Der p improved signs and symptoms in patients with AD.³⁷ SLIT was significantly effective in patients with local AR.³⁸ Multiple-allergen SCIT in children younger than 4 years failed to improve asthma-related outcomes except for asthma-related quality of life.³⁹ In patients with grass pollen-allergic rhinoconjunctivitis, intralymphatic immunotherapy resulted in a reduction in symptoms and a decrease in medication usage.⁴⁰ Polymerized allergens conjugated to nonoxidized mannan (PM-allergoids) are new AIT products targeting DCs to induce Treg cells. Safety and efficacy were confirmed for PM-allergoid-HDM administered as SCIT and SLIT. The treatment achieved clinical outcomes in a dose-dependent manner.⁴¹ Another study acknowledged the effectiveness (reduced symptoms and medications) and safety of a microcrystalline tyrosine-adsorbed Der p allergoid in patients with HDM-triggered allergic asthma.⁴² Accelerated schemes of SCIT using either an allergoid for grass pollen, birch, hazel, or mixed trees or as an aluminum hydroxide-adsorbed preparation of 6 kinds of grass pollen allergoid proved to be safe in patients with allergic rhinoconjunctivitis, with or without asthma.^{43,44}

Biologicals

Besides testing novel mAbs (fezakinumab, tezepelumab, astegolimab, itepekimab, risankizumab) in AD and severe asthma, recent studies report on a novel allergen-specific antibody approach on the evaluation of currently approved mAbs (benralizumab, dupilumab, omalizumab) in other allergic diseases (idiopathic anaphylaxis), age groups (children and adolescents), or essential outcomes (sense of smell).

A single subcutaneous dose of a specific mAb cocktail targeting Bet v 1 was administered in birch-allergic subjects. A decrease in total nasal symptom score and basophil responsiveness was observed in allergic subjects compared with placebo after 1 week, lasting for 2 months.⁴⁵ This study confirms that targeting specific epitopes is sufficient to block the allergic response and thus could become an alternative to AIT.

The management of idiopathic anaphylaxis remains a challenge because therapy for only acute events is available, and there is no prophylactic therapy. Based on the encouraging results with omalizumab facilitating OIT or preventing recurrent anaphylaxis and skin symptoms in patients with systemic mastocytosis, the anti-IgE mAb was tested in idiopathic anaphylaxis in a double-blind, placebo-controlled trial. Unfortunately, its efficacy was not significantly higher in patients compared with healthy controls.⁴⁶

Precision treatment in chronic rhinosinusitis with nasal polyps benefits from 2 regulatory-approved mAbs: dupilumab (targeting the IL-13/IL-4 pathway) and omalizumab (targeting the IgE pathway). However, eosinophilic inflammation has been implicated in the pathogenesis, severity, and treatment responsiveness of chronic rhinosinusitis with nasal polyps, and mepolizumab (anti-IL-5 mAb) proved effective in these patients. Improvement in nasal polyps score, nasal blockage, and sense of smell was reported with benralizumab (anti-IL-5R α mAb) as well.⁴⁷ This promising result supports the addition of another mAb targeting the IL-5 pathway to the therapeutic armamentarium in chronic rhinosinusitis with nasal polyps.

Following dupilumab's proof of efficacy and safety in the adult asthma population, a pivotal trial reported a significant reduction in asthma exacerbations in children with asthma aged 6 to 11 years, together with improvement in lung function, with no side effects.⁴⁸ This decisive trial led to the extension of approval for dupilumab for this age group, thus being the third mAb available for severe asthma in this population. Two *post hoc* analyses focused on adolescents with uncontrolled asthma and showed improvement in lung function and reduced levels of T2 biomarkers following dupilumab and good safety and efficacy profiles in the 2-year extension study (up to 3 years) of benralizumab treatment.^{49,50}

Several novel mAbs and small molecules have been tested in the last year for AD and for severe uncontrolled asthma (Table III).

Fezakinumab, an anti-IL-22 mAb, was well tolerated with clinical improvement in patients with moderate to AD.⁶⁰ In the AD group that responded to fezakinumab therapy, a transcriptomic signature for severe neutrophilic asthma was identified.

The fezakinumab-response signature, which included 296 down-regulated genes, was improved in patients with asthma.⁵⁶

Tezepelumab, a human mAb blocking the activity of thymic stromal lymphopoietin, reduced exacerbations and improved lung function in patients with severe asthma, independent of their blood eosinophils levels. Tezepelumab reduced eosinophilic airway inflammation, airway hyperresponsiveness to mannitol, and T2 biomarkers, including fractional exhaled nitric oxide and blood eosinophil count.⁵⁷ Itepekimab, an anti-IL-33 mAb, improved lung function and asthma control in patients with moderate to severe asthma.⁵¹ Itepekimab administration also effectively reduced exacerbations in former smokers with chronic obstructive pulmonary disease, indicating that the IL-33-driven pathogenetic mechanisms are relevant to different pulmonary disorders.⁵³ Astegolimab, a human IgG₂ mAb that selectively inhibits the IL-33 receptor, ST2, reduced the exacerbation rate in a broad population of patients with uncontrolled, severe asthma, including those who were eosinophil-low.⁵⁴

Risankizumab, an anti-IL-23 mAb, has proved ineffective in severe asthma. Worsening of asthma occurred earlier, and the exacerbation was more severe than in the placebo group. Activation genes of natural killer cells, T cytotoxic cells, and transcription factors of T_H1 and T_H17 cells were downregulated. These negative results question the potential role of IL-23 in T2 airway inflammation.⁵² An inhaled Janus kinase inhibitor was proved to reduce fractional exhaled nitric oxide in mild asthma.⁵⁵

REAL-WORLD EVIDENCE

RWE provides supportive data in areas in which data from clinical trials are missing or extremely rare. More often RWE is included in regulatory applications approving new therapies. RWE can assess clinical outcomes for unselected populations, potentially more useful in daily clinical decision making, ultimately supplying practical support, both in understanding safety and in efficacy.

A real-life study of fast-dissolving standardized quality HDM SLIT tablets reported an improvement in symptoms subjected to AR and/or asthma, with a safety profile consistent with data from controlled clinical trials.⁵⁸ Real-world preschool peanut OIT was proved effective after 1 year of maintenance: 78.6% had a negative oral food challenge, and 98.3% tolerated a cumulative dose of greater than or equal to 1000 mg. For those who reacted, their threshold increased sufficiently to protect against accidental exposures.⁶¹

The OmaBASE registry confirmed that in pediatric patients with severe cow's milk allergy, milk OIT initiated under omalizumab allows the desensitization of subjects even after omalizumab discontinuation.⁶² Using the Danish National Health Service Prescription Database and Statistics Denmark Database, the number of prescribed grass pollen AIT was linked to the age and education of citizens. It has been observed that SLIT fits better with the inequalities in AIT access.⁶³

Several severe asthma registries collect real-world data on patients with severe asthma receiving biological therapies in a standardized way. The UK Severe Asthma Registry reported insufficient asthma control, impaired lung function, and a large number of exacerbations.⁶⁴ The Belgian Severe Asthma Registry observed that decreased FEV₁ in severe eosinophilic asthma was linked with add-on therapy with mepolizumab (anti-IL-5).⁶⁵ The

Australian Registry reported a reduction in oral corticosteroid use with mepolizumab in patients with severe eosinophilic asthma.⁶⁶

The International Severe Asthma Registry noticed an overlap of biomarkers such as IgE, eosinophils, and fractional exhaled nitric oxide in severe asthma. Cluster analysis suggested different patterns of inflammatory pathways, guiding the targeted use of biologicals.⁶⁷

CLINICAL CARE PATHWAYS

These pathways create a consistent workflow for care delivery, including mHealth, which is a future-proof solution that can manage allergic diseases. mHealth biomarkers might help to monitor patients' disease—symptom-medication scores, enable stratification and follow-up in AIT, and monitor the efficacy and safety of therapies.

OIT for peanut allergy is the only regulatory-approved immunotherapy for food allergy. As it becomes more available, practitioners need to adjust to offer this treatment.⁶⁸

To date, there are no validated predictive models or tools for practitioners to estimate relative risks, especially anaphylaxis, for patients being considered for SCIT.⁶⁹ Most patients prefer their health care facility nearby; therefore, the transition of AIT care to the primary care setting is feasible and safe, and an electronic personal health environment could be helpful.⁷⁰ A clinical decision support system (@IT2020-CDSS) includes clinical history, diagnostic tests, and eDiary revised consensus on AIT prescriptions for seasonal AR.⁷¹

THE PREVENTIVE ROLE OF IMMUNOTHERAPY

AIT is considered to have been effective if it alleviated allergic symptoms, decreased medication use, improved the quality of life even after treatment cessation, and prevented the progression of AR to asthma and the onset of new sensitization. Long-term efficacy 2 years after AIT was stopped was evaluated for Japanese Cedar pollen SLIT tablets in patients aged 5 to 64 years. The primary end point was the total nasal symptom and medication score. The impact of AIT duration was also compared between the groups receiving 15 to 18 months of AIT versus 3 years. All groups receiving AIT showed a significant decrease in the total nasal symptom and medication score, both on treatment and after AIT cessation, with the most significant effect for the group receiving 3 years of AIT.⁷² Tolerance induction with T-cell epitopes was tested by several research groups. However, its preventive role against the onset of new sensitization has not yet been explored. As shown in an experimental model, early preventive administration of nonimmunogenic synthetic T-cell epitope-containing allergen peptides could prevent the development of allergen-specific IgE sensitization.⁷³ The preventive effect was specific to complete Bet v 1 allergen but not to the unrelated major grass pollen allergen Phl p 5. Although a promising approach, several important aspects need to be further clarified such as the dose, route, time window, and duration of administration. A recent systematic review and meta-analysis evaluated the preventive role of AIT for asthma development.⁷⁴ Besides randomized controlled trials, the analysis included evidence from nonrandomized studies of interventions and longitudinal observational studies. Random-effects analysis showed a significant decrease in the risk of developing asthma by 25% (risk ratio, 0.75; 95% CI, 0.64-0.88). However, this effect was not significant

in the sensitivity analysis. Subgroup analysis showed a remarkable preventive effect of AIT in children when completing 3 years of therapy and in monosensitized patients.

The impact of systemic treatments on the skin transcriptome was explored in patients with AD enrolled in the TREATgermany registry.⁷⁵ Cyclosporine led to a more pronounced global transcriptome reversion and normalized T_H17 cell/IL-23 signaling, whereas dupilumab led to a more robust increase in the level of epidermal differentiation markers. Both treatments strongly decreased levels of type 2 markers. However, the overall profile under the systemic treatment was still profoundly different from that of healthy skin. Lower levels of IL-4RA and IL-13 and high IL-36A expression were related to a more robust clinical response to dupilumab.

FUTURE PERSPECTIVES: NOVEL TOOLS FOR IMMUNOTHERAPY

New techniques contribute to significant advances in the field of immunotherapy, enabling the direct interaction with immunoregulatory mechanisms or pathophysiological mechanisms at the tissue level.

Nanoparticles deliver messenger RNA, small-interfering RNA, plasmid DNA, proteins, and peptides or clustered regularly interspaced short palindromic repeat (CRISPR) drugs. Pulmonary delivery is of particular interest for developing next-generation multifunctional combination therapies, mainly including image-guided therapy and real-time disease monitoring.^{76,77} Recently, a GATA3-targeting nucleic acid nanocapsule system for *in vivo* gene regulation in asthma was developed. It is constructed of cross-linked peptide surfactants that undergo degradation and release DNA-zyme surfactant conjugates under proteolytic enzymes. The compound is uptaken by PBMCs, especially CD4⁺ cells, to achieve the GATA3 messenger RNA cleavage and modulation of the T2 phenotype. In the murine model of HDM-triggered asthma, DNazyme-nanocapsule administration protected against severe allergic lung inflammation.⁷⁸

Other engineered approaches, which use the genetic modification of polyclonal Treg cells with chimeric antigen receptor (CAR), provide an abundance of Treg cells of the desired antigen specificity. CARs are recombinant receptors targeting specific surface antigens.^{59,79} Treg-cell therapy by inserting IL-10 or TGF- β or removing the IL-17, IL-4, IFN- γ , and IL-6 genes can be applied using CRISPR or other gene editing tools or nucleases.⁸⁰ Treg cells integrated with CARs containing CD28-CD3 ζ and CARs targeting IgE receptors have been applied for the treatment of asthma.⁸¹

Because aberrant epigenetic modifications are reversible, epigenetic therapy plays a role in modulating immune responses. The first drugs targeting the metabolic basis of epigenetic effects have been implemented in clinics. CRISPR/dead protein 9 system (dCas9)-based epigenetic editing is a promising approach for targeted therapy.⁸² dCAS9 was used to target epigenetic editing proteins to the *SPDEF* promoter in human lung epithelial cells, leading to potential alteration in phenotype by long-term downregulation of mucus-related gene expression.^{83,84}

Exosomes, which belong to extracellular vesicles along with microvesicles and apoptotic bodies, have been described as modulators in different inflammatory diseases. Exosomes could be engineered as therapeutic agents in AIT, with the significant advantage of shielding allergens from IgE-sensitized high-affinity

receptor for the Fc region of IgE expressed by mast cells and basophils. Tolerosomes are exosomes derived from IL-2-primed tolerogenic DCs or mesenchymal stem cells, which promote Treg cells. B-cell-derived exosomes modulating IgE-facilitated antigen presentation are of notable interest because of the much lower risk of inducing systemic reactions.⁸⁵ Exosomes containing miRNAs provide another novel tool to treat allergic diseases. miRNAs function as posttranscriptional regulators, controlling various cellular processes, and might show great potential in AIT.⁸⁶

Cellular therapies using airway basal cells are currently being developed. A directed differentiation protocol enabling the generation of airway basal cells from human-induced pluripotent stem cells has been tested. Airway basal cells recapitulate hallmark stem cell properties of primary basal cells, including self-renewal and multilineage differentiation, share key physiologic and biologic features with human airway epithelium, and can be used to regenerate airway epithelium *in vivo*.⁸⁷⁻⁸⁹

Recently, the concept of disruptive “efficiency,” which relates the half-maximal disruptive concentration to the affinity for free IgE, was introduced.⁹⁰ This relates to kinetic mechanisms that involve the facilitated dissociation of targeted complexes. During facilitated dissociation, “disruptive” inhibitors engage targets that are sequestered in stable macromolecular complexes, accelerate their dissociation, and inactivate them rather than simply blocking interactions between proteins. Omalizumab displays weak disruptive activity at high concentrations, whereas ligelizumab (anti-IgE mAb) does not display any disruptive activity, despite its higher affinity for IgE. A more potent omalizumab variant featuring fast dissociation of the receptor-bound IgE and desensitization of effector cells has been described.⁹¹

CONCLUSIONS

Immunotherapy, delivered as AIT, mAb, or small molecules, is the fundamental model of the personalized approach to allergy management. Significant progress has been achieved, especially in the application of precision medicine by phenotyping and endotyping based on mHealth and biomarker approaches aiming at the better prospective and retrospective stratification of patients according to their theratypes. These tools show great promise for clinical practice. Novel approaches to data analysis combining pivotal controlled clinical trials with good-quality RWE derived from disease registries or well-conducted interventions are postulated to improve the quality of evidence, which would be of great value to regulatory bodies.

Recent developments in immunotherapy by application of innovative compounds and preparations or modified protocols might significantly improve the immunotherapy efficacy and patients' compliance by reducing therapy duration and costs.

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