Update on allergy immunotherapy: American Academy of Allergy, Asthma & Immunology/European Academy of Allergy and Clinical Immunology/PRACTALL consensus report

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Allergy immunotherapy (AIT) is an effective treatment for allergic asthma and rhinitis, as well as venom-induced anaphylaxis. In addition to reducing symptoms, AIT can change the course of allergic disease and induce allergen-specific immune tolerance. In current clinical practice immunotherapy is delivered either subcutaneously or sublingually; some allergens, such as grass pollen, can be delivered through either route, whereas others, such as venoms, are only delivered subcutaneously. Both subcutaneous and sublingual immunotherapy appear to have a duration of efficacy of up to 12 years, and both can prevent the development of asthma and new allergen sensitivities. In spite of the advances with AIT, safer and more effective AIT strategies are needed, especially for patients with asthma, atopic dermatitis, or food allergy. Novel approaches to improve AIT include use of adjuvants or recombinant allergens and alternate routes of administration. As part of the PRACTALL initiatives, the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology nominated an expert team to develop a comprehensive consensus report on the mechanisms of AIT and its use in clinical practice, as well as unmet needs and ongoing developments in AIT. This resulting report is endorsed by both academies. (J Allergy Clin Immunol 2013;131:1288-96.)

Key words: *Allergen immunotherapy, atopic disease, immune tolerance*

Various terms have been used to describe immunotherapy for treating allergy. Examples are *allergen-specific immunotherapy*, *specific immunotherapy*, *allergen immunotherapy*, and *allergy immunotherapy* (AIT). Because there is a need for uniformity in naming, and because immunotherapy can include both allergen-specific and nonspecific approaches, we propose that the term allergy immunotherapy be universally used to refer to the class of therapies that aim to induce immune tolerance to allergens.

A key feature of AIT is that it can change the course of disease by altering the underlying natural history. Currently, 2 types of AIT are in clinical practice: subcutaneous immunotherapy (SCIT)

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Abbreviations used
AIT: Allergy immunotherapy
OIT: Oral immunotherapy
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
TLR: Toll-like receptor
Treg: Regulatory T

and sublingual immunotherapy (SLIT). Some allergens, such as grass pollen, can be delivered through either route, whereas others, such as venoms, are only delivered subcutaneously. Several novel AIT approaches are being evaluated in clinical trials.

With the goal of creating a comprehensive review of AIT, the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology nominated experts to collaborate as part of the PRACTALL initiatives. This consensus report describes the mechanisms of AIT and its use in clinical practice, differences in practices between Europe and the United States, and priorities for addressing unmet needs in specific indications and with specific therapeutic approaches.

MECHANISMS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

Very early desensitization

The ultimate goal for the therapy of immunologic diseases (eg, allergy), autoimmunity, and organ transplantation is to induce immune tolerance, a change in the immune response to specific antigens such that discontinuation of the therapy results in sustained long-lasting therapeutic benefits.[1,2] Peripheral T-cell tolerance is crucial for such benefits.[3]

An initial step in AIT is desensitization of FcεRI-bearing mast cells and basophils. The mechanism of this desensitization is not fully elucidated, although rapid upregulation of the histamine 2 receptor, which is a major suppressor of basophil activation, occurs within the first 6 hours of the build-up phase of venom AIT (Fig 1).[4]

T-cell responses

Multiple mechanisms related to T- and B-cell regulation play a role in allergen tolerance.[5] Basophil and mast cell desensitization is followed by a T-cell–tolerant state.[1] Allergen-specific peripheral T-cell tolerance mediated by IL-10, TGF-β, and other suppressive factors causes deviation toward a regulatory T (Treg) cell response, which leads to a normal, healthy immune response to mucosal antigens. IL-10 originates from antigen-specific T cells and activated $CD4^+CD25^+$ T cells, as well as monocytes and B cells.[6,7] This IL-10 increase is similar to the mechanisms of allergen tolerance observed in high-dose allergen exposure models, such as beekeepers and cat owners. It is possible to purify live IFN-γ–, IL-4–, and IL-10–secreting allergen-specific $CD4^+$ T cells that resemble T_H1, T_H2, and type 1 Treg–like cells, respectively, to investigate allergen-specific T-cell responses. Healthy and allergic subjects exhibit all 3 subsets, although in different proportions. In healthy subjects IL-10–secreting T_R1 or IL-10–Treg cells are the dominant subset for common environmental allergens, whereas in allergic subjects allergen-specific IL-4–secreting T cells (T_H2-like cells) exist at a high frequency.[8,9] Hence a change in the dominant subset toward IL-4 might lead to the development of allergy, whereas IL-10 dominance leads to recovery. Peripheral tolerance to allergens involves multiple suppressive factors, such as IL-10, TGF-β, cytotoxic T lymphocyte–associated antigen 4, and programmed death-1.[8] In contrast, breaking of peripheral T-cell tolerance to allergens can lead to the development of allergies. Mechanisms for breaking tolerance can include activity of myeloid dendritic cells, Toll-like receptor (TLR) 4 or TLR8, and the proinflammatory cytokines IL-1β or IL-6.[10]

TGF-β production increases during AIT for mucosal allergies but not during AIT for venom allergy. Differences in immune responses to venoms versus aeroallergens might be due to different routes of natural allergen exposure. In human subjects the T cells that are predominant during AIT and natural antigen exposure are T_R1 or IL-10–Treg cells that are enriched within $CD4^+CD25^+$ cells.[11-14] During grass pollen immunotherapy, numbers of forkhead box protein 3–positive $CD25^+$ Treg cells are increased in the skin during late-phase responses and in the nasal mucosa as the affected organ.[15,16] Sublingual grass pollen immunotherapy is associated with increases in sublingual forkhead box protein 3–expressing cell numbers and increased allergen-specific IgG_4 levels, IgA levels, and serum inhibitory activity for IgE-facilitated allergen binding to B cells.[17] In human subjects Treg cells appear to play a major role in inhibiting allergic disorders. In asthmatic patients IL-10 levels in the bronchoalveolar lavage fluid are less than those in healthy control subjects, and T cells express less IL-10 mRNA.[18,19] In patients who have undergone AIT with grass pollen, IL-10 mRNA expression increases in nasal and mucosal skin tissue during the pollen season.[20,21] In parallel, an increase in IFN-γ levels has been shown in some studies.[20,21]

Allergen-specific IgE and IgG_4 responses

Although AIT rapidly induces peripheral T-cell tolerance, there is no evidence that it induces B-cell tolerance.[1] Natural exposure to a relevant allergen is often associated with increased IgE synthesis. Serum-specific IgE levels often transiently increase after AIT and then gradually decrease over months or years of continued treatment.[22-24] In pollen-sensitive patients who have undergone AIT and become desensitized, serum allergen-specific IgE titers do not increase during the pollen season.[25,26] Changes in IgE levels cannot account for diminished responsiveness to specific allergen after AIT because the decrease in serum IgE levels is late, relatively small, and poorly correlated with clinical improvement after AIT.

Increases in specific IgG_4 levels accompany clinical improvement with AIT.[27,28] IgG_4 is considered a blocking antibody, which suggests that IgG_4 inhibits allergen-induced and IgE-mediated release of inflammatory mediators from basophils and mast cells, IgE-facilitated allergen presentation to T cells, and allergen-induced boost of memory IgE production during allergen exposure. Grass pollen immunotherapy induces allergen-specific, IL-10–associated "protective" IgG_4 responses in which IgG_4-dependent blocking of IgE binding to B cells occurs.[21]

IL-10 and Treg cells potently suppress both total and allergen-specific IgE and simultaneously increase IgG_4 production.[6,29] Thus in addition to generating tolerance in T cells, IL-10 regulates specific antibody isotype formation and skews the specific response from an IgE- to an IgG_4-dominated phenotype. In a study of AIT for house dust mite allergy, after 70 days, specific IgE

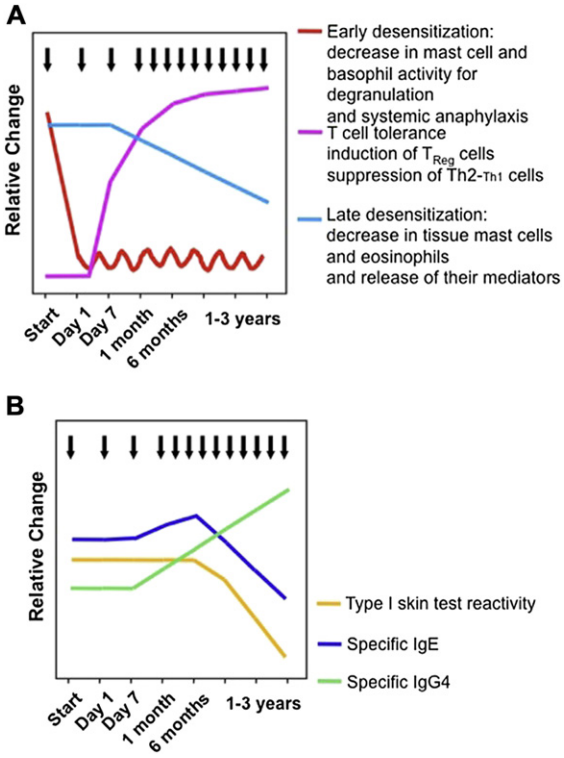

FIG 1. Immunologic changes during the course of AIT. **A,** Although there is significant variation between subjects and protocols, an early decrease in mast cell and basophil degranulation and decreased tendency for systemic anaphylaxis is observed immediately after the first administration of allergens with a native-like structure. This is followed by generation of allergen-specific Treg cells and suppression of allergen-specific T_H1 and T_H2 cells and possibly other effector cells. **B,** An early increase and a very late decrease in specific IgE levels are observed. IgG_4 levels show a relatively early increase that is dose dependent. In some studies allergen-specific IgG_1 and IgA levels also increase. A significant decrease in the allergen-specific IgE/IgG_4 ratio occurs after several months. A significant decrease in type I skin test reactivity is also observed relatively late in the course of specific immunotherapy. After a few months, a decrease in tissue mast cell and eosinophil numbers and release of their mediators is observed, as well as a decrease in the late-phase response. These effects are partially demonstrated in SLIT and are rather weak compared with those seen in SCIT. Novel AIT approaches might or might not show these effects, although they still can be effective.

levels did not change, although specific IgA, IgG_1, and IgG_4 levels were significantly increased.[7] The increase in specific IgA levels in serum coincided with increased TGF-β levels in T-cell cultures, and the increase in serum IgG_4 levels coincided with increased IL-10 levels in T-cell cultures. These changes are consistent with the roles of IgA and TGF-β, as well as IgG_4 and IL-10, in peripheral mucosal immune responses to allergens in healthy subjects.[6]

Regulation of mast cells, basophils, and eosinophils

IL-10 and Treg cells efficiently modulate the thresholds for mast cell and basophil activation and decrease IgE-mediated histamine release.[30] In addition, IL-10 downregulates eosinophil function and activity and suppresses IL-5 production by human T cells.[31] Treg cells directly inhibit the FcεRI-dependent mast cell degranulation through Treg cell–mast cell contact, which leads to increased cyclic AMP concentrations and reduced Ca^{++} influx. In addition, OX40–OX40 ligand interaction plays an important role.[32] Recently, mast cells have been reported to have an immunoregulatory role in downregulating inflammatory responses in which IL-10 plays an important role.[33,34]

Although the ultimate goal of AIT is to change the immune response to allergens such that benefits last after discontinuation of therapy, it is not clear whether this actually occurs with all successful therapies because exposure to environmental allergens can vary. For example, many patients who receive grass pollen AIT continue to have environmental exposure to the allergen even after therapy is discontinued. Similarly, the long-term continuation of peripheral T-cell tolerance to venom allergens requires continuous exposure in nonallergic beekeepers.[35] This sustained exposure likely aids in maintaining tolerance. Thus it is possible that for certain allergy indications, such as food allergy, maintaining immune tolerance is only feasible if allergen exposure is ongoing.

CURRENT STATUS OF ALLERGEN-SPECIFIC IMMUNOTHERAPY

Indications

The 2 most commonly prescribed routes for AIT are SCIT and SLIT. Route selection varies considerably depending on several factors, including vaccine availability or approval, geographic location, cost, and the patient's characteristics or the physician's or patient's preference. For allergic asthma and rhinitis, numerous double-blind, placebo-controlled trials have confirmed that SLIT and SCIT are effective in reducing symptom scores and medication use, improving quality of life, and inducing favorable changes in specific immunologic markers.[36] Tables E1 and E2 in this article's Online Repository at www.jacionline.org contain detailed information regarding the effects of AIT for the treatment of allergic respiratory disease. Both SLIT and SCIT have shown promising results in reducing topical corticosteroid use and improving SCORAD scores in patients with atopic dermatitis.[37] SCIT has also been shown to be efficacious in preventing venom-induced anaphylaxis. SCIT has been evaluated for treating food allergy to peanuts, but anaphylactic reactions were reported,[38,39] and the approach was abandoned.

Side effects

SCIT-induced adverse reactions can be local or systemic. The severity of SCIT-induced systemic reactions range from mild symptoms[40] to life-threatening anaphylaxis and even death. In a 3-year survey between 2007 and 2009, which included approximately 8 million injection visits per year, the reported rate of systemic reactions to SCIT was approximately 0.1% of injections, with no fatalities reported.[41,42] The majority of systemic reactions (86%) occurred within 30 minutes after SCIT administration.[42] Most delayed-onset systemic reactions were mild, but severe delayed-onset reactions did occur.[42,43] Given the concern regarding systemic reactions, practice guidelines recommend that patients receive SCIT in a supervised medical facility and be monitored for 30 minutes after the injection.[44,45]

In some parts of the world, mainly Europe, SLIT represents 80% or more of new AIT prescriptions.[46] SLIT has a better safety profile than SCIT, and this advantage allows for home administration.[47] The most common adverse effects with SLIT are local reactions (oromucosal pruritus or mild local edema), which

TABLE I. Comparison of AIT in the United States and Europe

	United States	Europe
	Regulatory agency: FDA	Regulatory agency: EMA
Standardization		
Method	ID_{50}EAL or major allergen content	Nordic
Test technique	Intradermal	Percutaneous
End point	Extract dilution that produces sum of erythema of 50 mm or content concentration	Extract dilution that produces wheal = histamine control
Potency determination	Comparison with CBER reference control	Compared with manufacturer's in-house reference
Future focus	Overall allergenicity (multiplex microbead array)	Major allergen content
Potency units	BAU, wt/vol, PNU, FDA units of major allergen for ragweed and cat	Varies: each company essentially has its own potency units (eg, IR and SQ-T); some provide μg of major allergen.
Extract formulation		
Location	Prepared in clinicians' offices	Prepared at extract manufacturer's site
Number of allergens	Multiple	Generally 1
Allergen extract types	Aqueous and glycerinated unmodified extracts, alum-precipitated depot extracts (~75,000 to 150,000 patients*)	Approximately 100% depot extract, 20% allergoid
SLIT	No FDA-approved formulation	Varies with country, but solution and tablets are available; some are registered.
Conventional updosing schedule for SCIT	1-3 times a week	Once weekly
SCIT maintenance schedule (duration)	Every 2-4 wk (3-5 y)	Every 4-8 wk (3-5 y)
Accelerated schedules	Venom cluster, rush Aeroallergen cluster, rush (rarely used)	Venom cluster, rush, ultrarush Aeroallergen cluster, rush (rarely used)
Reimbursement	Covered as a medical service by government and private insurers; prices can be negotiated, but private insurers often use government schedule.	Varies; extract companies negotiate payment with each country.

Modified with permission from Cox and Jacobsen.[46]

BAU, Bioequivalent allergy units; *CBER*, Center for Biologics Evaluation and Research; *EMA*, European Medicines Agency; *FDA*, US Food and Drug Administration; *ID_{50}EAL*, intradermal dilution for 50-mm sum of erythema; *IR*, index of reactivity; *PNU*, protein nitrogen unit; *SQ-T*, standardized quality tablet.

*Of an estimated 3 million patients receiving AIT in the United States; the estimate is based on extract manufacturer's sales (Greg Plunkett, PhD, ALK-Abelló, written communication, September 29, 2012).

generally occur within the first few days of treatment and subsequently resolve without medical intervention as treatment is continued. SLIT-induced systemic reactions are uncommon, and no SLIT-related fatalities have been reported.[47,48] With SLIT, no clear risk factors for systemic reactions have been established.[49]

Dosing

For many allergens, effective SLIT or SCIT doses have not been established. With grass pollen, the effective cumulative SLIT doses appear to be as high as 20 to 30 times greater than the effective SCIT doses; this means a daily SLIT dose is roughly equivalent to a monthly SCIT dose. Almost all clinical studies of SCIT and SLIT have evaluated therapy with a single allergen and not multiple allergens. In most European practices single-allergen SCIT or SLIT is typically prescribed.[46,49] However, in the United States SCIT is commonly performed with multiple allergens (Table I), a practice that is supported by some older studies.[46,49,50] Multiallergen SLIT has not been well studied, and its use might be limited by the increased cost of needing higher doses and the inconvenience of taking multiple tablets.

Efficacy

The effect sizes for both SCIT and SLIT are summarized in Tables E1 and E2. Several years of treatment with SCIT and SLIT has a duration of efficacy of 7 to 12 years after discontinuation.[51-56] AIT can be just as effective as pharmacologic medications in reducing symptoms during treatment. In grass pollen–induced allergic rhinitis, SCIT has a greater mean relative clinical effect in reducing nasal and ocular symptom scores than the antihistamine desloratadine.[57] SCIT also has a greater mean relative clinical effect for reducing nasal symptoms than the corticosteroid mometasone or the leukotriene receptor antagonist montelukast. Evidence from recent, large-scale clinical trials suggests that SLIT has much the same relative clinical effect as SCIT in this context. In addition to treating allergy symptoms, SCIT and SLIT appear to prevent progression of allergic rhinitis to asthma and the development of new allergen sensitivities in monosensitized subjects.[58] Studies comparing cost-effectiveness between patients treated for 3 years with AIT versus those treated with pharmacotherapy alone have indicated that AIT might be associated with cost savings as high as 80% 3 years after completion of treatment.[59]

FUTURE OF AIT

Although SCIT and SLIT benefit many patients, not all patients will see improvement with these therapies, and each carries the risk of anaphylaxis. In addition, adherence with current AIT regimens is low,[59-61] possibly because of the number of administrations and the duration of the therapeutic course. Thus there is a need for safer and more effective AIT strategies, especially for patients with asthma, atopic dermatitis, or food allergy. Novel AIT approaches have been lacking in part because of the high costs of

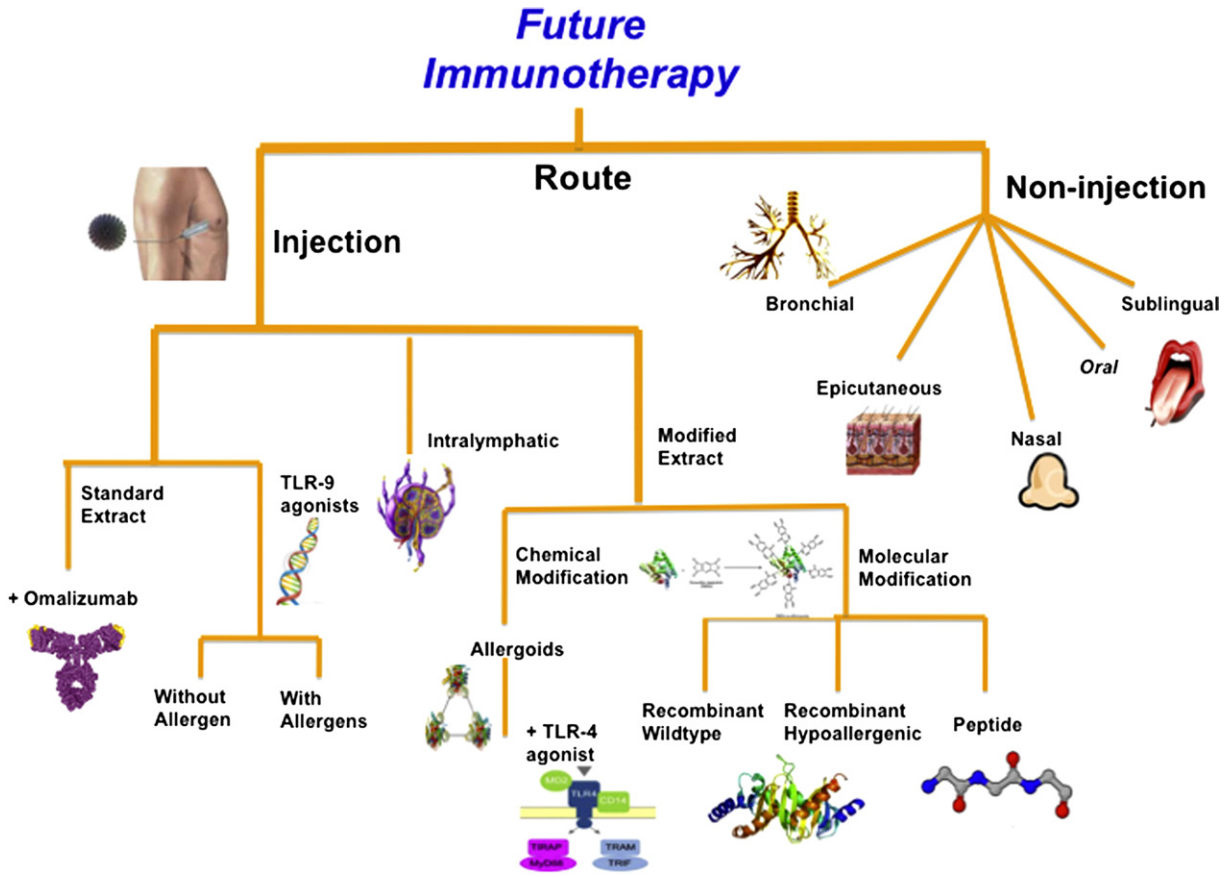

FIG 2. Novel approaches to AIT.

development and the relatively small market. Development challenges are compounded by strict and sometimes inconsistent and cumbersome regulatory approval processes, the lack of predictive phenotypes or measurable biomarkers characterizing responders versus nonresponders, and the use of varied parameters to assess response, which make it difficult to compare data from different trials.

Several novel immunotherapeutic approaches might improve the immunogenicity of AIT without increasing its allergenicity, thereby improving the risk/benefit profile.[3] Such approaches have included adding therapy to standard AIT, altering the allergen extract, using novel adjuvants, or changing the mode of delivery of the allergen extract (Fig 2). Adding omalizumab to SCIT improves its safety and tolerability during build-up, the likelihood of the patient reaching the maintenance phase, and the therapy's overall effectiveness.[62-64]

Cloning of allergen proteins with use of recombinant DNA technology enabled the production of vaccines that have well-defined molecular, immunologic, and biological characteristics.[65] Moreover, genetic engineering enables modifications of molecular structure that can reduce allergenic activity, increase immunogenicity, or both.[66]

Innate immune response inducers, such as TLR agonists, can skew the cytokine balance from T_H2 to T_H1, thereby reducing symptoms of allergic disease. Agonists for 4 TLRs (TLR1, TLR4, TLR8, and TLR9) have been studied in clinical trials for allergic diseases. Of these, ligands for TLR4 and TLR9 with and without allergen have been studied most. TLR4 (CD284) is expressed on the cell surface with the adaptor molecule CD14. Monophosphoryl lipid A is derived from LPS found on the gram-negative bacteria *Salmonella minnesota* and is used as an adjuvant that binds to TLR4. Pollen extracts that are chemically modified (allergoids) and combined with a monophosphoryl lipid A adjuvant have been used in Europe and Canada as a preseasonal, ultrashort SCIT course consisting of 4 weekly subcutaneous injections.[67]

Short segments of DNA with CpG motifs, which are TLR9 agonists, have been used in many different modalities as immunotherapy. Covalently linking B-type CpG to major allergens initially looked promising,[68] but large multicenter studies did not meet efficacy end points,[69] and this approach has been abandoned. A-type CpG motifs with and without allergen have also been studied. A-type CpG molecules are more potent inducers of IFN-α than B-type CpGs, and their unstable phosphodiester backbones can be stabilized by association with virus-like particles, such as the bacteriophage Qb coat protein. This approach, used with and without allergen, has demonstrated both efficacy and safety in several clinical trials involving both patients with allergic rhinitis and those with asthma.[70,71] Peptides of grass pollen or cat allergen have been fused to an immunogenic carrier element from hepatitis B virus, and a phase 2b study of the grass pollen vaccine (BM32) is currently in progress. Fusing allergen to a translocation sequence (TAT) and to part of the human invariant chain dramatically increases the efficiency of allergen presentation and has been used to generate a modular antigen transporter vaccine. Administration of fusion sequences through intralymphatic injection, which results in an enhanced immune response,

has been evaluated for cat allergy. In a clinical study 3 monthly intralymphatic injections of MAT–Fel d 1 increased nasal tolerance 74-fold versus placebo.[72] In addition, the MAT–Fel d 1 injections led to Treg cell responses and also increased cat dander–specific IgG_4 levels more than 5-fold. The IgG_4 response positively correlated with IL-10 production.

Establishing the protein molecular structure, as well as the immune function, of a natural allergen and its epitopes enables cloning of allergen proteins with use of recombinant DNA technology. Moreover, genetic engineering enables modifications of the structure of either whole allergens or their key T- or B-cell epitopes as a novel approach for hypoallergenic AIT.

Another procedure involves fusing major allergens, such as bee venom Api m 1 and Api m 2, in a way that deletes the B-cell epitopes but preserves the T-cell epitopes.[73] A different strategy involves the use of peptide fragments corresponding to T-cell epitopes of specific allergens that are too small to bind IgE but induce immunologic tolerance.[74] There are a number of clinical trials ongoing with these approaches using both SCIT and SLIT protocols.

AIT delivery through the oral, nasal, bronchial, epicutaneous, intraepithelial, or intra–lymph node routes has been investigated.[75-77] Intranasal and intrabronchial immunotherapy are not commonly used because of administration-associated local symptoms. Intralymphatic AIT has shown benefit with several allergens, including cat and grass pollen.[71,72]

For food allergy, oral immunotherapy (OIT) and SLIT have been successful in inducing desensitization to allergens, such as milk, peanut, eggs, and hazelnut, in small clinical trials.[78-89] With OIT, the majority of adverse reactions have been oral or pharyngeal, with up to 15% of subjects having significant gastrointestinal side effects, but epinephrine use for more severe reactions has been reported.[78,79,84,85,90] OIT and SLIT study protocols have only been conducted in highly controlled settings in which therapy for severe reactions was readily available. Neither OIT nor SLIT is recommended for widespread clinical use for food-related allergy.[91] For OIT and SLIT to become recommended as standards of care for food allergy, several facets of their use will need to be better defined, such as the relative risks of therapy versus allergen avoidance, optimal dosing regimens, and appropriate patient populations.

Examples of additional immunotherapy approaches being evaluated for food allergy are diets containing extensively heated (cooked) milk and egg, treatments with modified antigens, epicutaneous administration of allergen, or combining OIT with anti-IgE mAbs.[92,93]

UNMET CLINICAL NEEDS IN AIT

AIT has reached a good level of robustness as an evidence-based therapy. However, there are still unmet needs in terms of administering and evaluating both existing and novel therapies. They are as follows.

Clinical trial development

- Standardization and validation of clinical outcome measures that are accepted by academic, research, industry, and regulatory groups.
- Proper study designs for evaluating AIT for nonrespiratory allergies.
- Validation and acceptance of allergen chambers as suitable surrogates for natural allergen exposure.
- Well-designed postmarketing tools to assess the effectiveness of AIT in real life (eg, patient-related outcomes).

Patient selection

- Development of methods for identifying AIT-responsive and nonresponsive endotypes and phenotypes.
- Identification of AIT-responsive phenotypes of asthma and atopic dermatitis.

Biomarkers

- Identification and validation of biomarkers that are predictive of clinical response.

Adherence to AIT

- Development of methods for improving patient adherence over the long term.

Disease modification

- Elucidation of the mechanisms by which AIT modifies underlying atopic disease through well-designed studies.
- Better definitions of the long-term immunotolerogenic effects of AIT.

Optimization of current AIT

- Evaluation and confirmation of the regimens likely to generate optimal clinical outcomes (eg, dosing, build-up strategies, and duration of therapy).

New approaches

- Evaluation and confirmation of the efficacy and safety of AIT with adjuvants, recombinant or modified allergen molecules, peptides, and new routes of AIT (eg, intralymphatic or epicutaneous) in properly designed and powered studies.

Safety

- Development of a depot allergen extract and premedication regimens that reduce the rate of systemic reaction with SCIT.
- Comparisons of conventional SLIT updosing with maintenance with initiation of SLIT at maintenance doses.
- Validation and standardization of contraindications and recommendations for modifications in AIT dosing.
- Development of newer AIT approaches that are safer than SCIT and SLIT.

Economics

- Comparisons of both direct and indirect long-term (>3 years) economic outcomes of AIT with other therapies.

Standardization of extracts

- Adoption of a uniform measure of allergen extract potency.
- Standards for assessment of major allergen content.

Multiple-allergen extracts

- Well-designed studies of efficacy of multiple-allergen extracts for SCIT and SLIT.

Allergen extract quality

- Improved potency of certain commercial extracts (eg, dog, cockroach, and fungi) that often lack effectiveness.

Extract stability and compatibility

- Evaluations and reports on the stability of extract dilutions, mixtures, or both over time to better guide AIT regimens.

Regulatory guidance

- Consistent, standardized, and feasible assessments for AIT approval worldwide.

CONCLUSION

AIT is effective in reducing symptoms of allergic asthma and rhinitis, as well as venom-induced anaphylaxis. In addition, AIT modifies the underlying course of disease. However, AIT remains a niche treatment secondary to symptomatic drugs because of its cost, long duration of treatment, and concerns regarding safety and effectiveness. In both the United States and Europe the treatment population is underserved. Further research is needed to develop novel therapies and optimize current ones. To these ends, having harmonized efficacy criteria, regulatory guidance, and reagent standardization would be of benefit. Also of benefit would be having biomarkers and phenotypes to predict the likelihood of response. As the mechanisms underlying disease continue to be elucidated, it is expected that novel strategies for AIT will continue to emerge.

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TABLE E1. Symptom scores

Disease	Author	Studies (no.)	Population	Participants		Effect size, SMD (95% CI)*	Heterogeneity I^2†
				Active (no.)	Placebo (no.)		
SCIT							
Rhinitis	Calderon,[E1] 2007	15	Adults	597	466	−0.73 (−0.97 to −0.50)	63%
Asthma	Abramson,[E2] 2010	34	Adults and children	727	557	−0.59 (−0.83 to −0.35)	73%
SLIT							
Rhinitis	Wilson,[E3] 2003	21	Adults and children	484	475	−0.42 (−0.69 to −0.15)	73%
Rhinitis	Penagos,[E4] 2006	10	Children	245	239	−0.56 (−1.01 to −0.10)	81%
Rhinitis	Radulovic,[E5] 2011	49	Adults and children	2333	2256	−0.49 (−0.64 to −0.34)	81%
Asthma	Calamita,[E6] 2006	9	Adults and children	150	153	−0.38 (−0.79 to 0.03)	64%
Asthma	Penagos,[E7] 2008	9	Children	232	209	−1.14 (−2.10 to −0.18)	94%
Conjunctivitis	Calderon,[E8] 2011	36	Adults and children	1725	1674	−0.41 (−0.53 to −0.28)	59%
House dust mites	Compalati,[E9] 2009	8	Adults and children	194	188	−0.95 (−1.77 to −0.14)	92%
Grass allergens	Di Bona,[E10] 2010	19	Adults and children	1518	1453	−0.32 (−0.44 to −0.21)	56%

*Effect size (SMD): poor, <−0.20; medium, −0.50; high, >−0.80.

†Heterogeneity (I^2) = 0% to 40%, might not be important; 30% to 60%, might represent moderate heterogeneity; 50% to 90%, might represent substantial heterogeneity; 75% to 100%, considerable heterogeneity.

TABLE E2. Medication scores

Disease	Author	Studies (no.)	Population	Participants		Effect size, SMD (95% CI)*	Heterogeneity I^2†
				Active (no.)	Placebo (no.)		
SCIT							
Rhinitis	Calderon,[E1] 2007	13	Adults	549	414	−0.57 (−0.82 to −0.33)	64%
Asthma	Abramson,[E2] 2010	20	Adults and children	485	384	−0.53 (−0.80 to −0.27)	67%
SLIT							
Rhinitis	Wilson,[E3] 2003	17	Adults and children	405	398	−0.43 (−0.63 to −0.23)	44%
Rhinitis	Penagos,[E4] 2006	7	Children	141	138	−0.76 (−1.46 to −0.06)	86%
Rhinitis	Radulovic,[E5] 2011	38	Adults and children	1737	1642	−0.32 (−0.43 to −0.21)	50%
Asthma	Calamita,[E6] 2006	6	Adults and children	132	122	−0.91 (−1.94 to 0.12)	92%
Asthma	Penagos,[E7] 2008	7	Children	192	174	−1.63 (−2.83 to −0.44)	95%
Conjunctivitis	Calderon,[E8] 2011	13	Adults and children	560	478	−0.10 (−0.22 to 0.03)	34%
House dust mites	Compalati,[E9] 2009	4	Adults and children	89	86	−1.88 (−3.65 to −0.12)	95%
Grass allergens	Di Bona,[E10] 2010	17	Adults and children	1428	1358	−0.33 (−0.50 to −0.16)	78%

*Effect size (SMD): poor, <−0.20; medium, −0.50; high, >−0.80.

†Heterogeneity (I^2) = 0% to 40%, might not be important; 30% to 60%, might represent moderate heterogeneity; 50% to 90%, might represent substantial heterogeneity; 75% to 100%, considerable heterogeneity.