

Immunotherapy: What lies beyond

Thomas B. Casale, MD,^a and Jeffrey R. Stokes, MD^b *Tampa, Fla, and Omaha, Neb*

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Allergen immunotherapy has been used to treat allergic diseases, such as asthma, allergic rhinitis, and venom allergy, since first described over a century ago. The current standard of care in the United States involves subcutaneous administration of clinically relevant allergens for several months, building up to eventual monthly injections for typically 3 to 5 years. Recent advances have improved the safety and efficacy of immunotherapy. The addition of omalizumab or Toll-like receptor agonists to standard subcutaneous immunotherapy has proved beneficial. Altering the extract itself, either through chemical manipulation producing allergoids or directly producing recombinant proteins or significant peptides, has been evaluated with promising results. The use of different administration techniques, such as sublingual immunotherapy, is common in Europe and is on the immediate horizon in the United States. Other methods of administering allergen immunotherapy have been studied, including epicutaneous, intralymphatic, intranasal, and oral immunotherapy. In this review we focus on new types and routes of immunotherapy,

exploring recent human clinical trial data. The promise of better immunotherapies appears closer than ever before, but much work is still needed to develop novel immunotherapies that induce immunologic tolerance and enhanced clinical efficacy and safety over that noted for subcutaneous allergen immunotherapy. (*J Allergy Clin Immunol* 2014;133:612-9.)

Key words: Immunotherapy, allergy, asthma, omalizumab, allergens, recombinant, peptide, epicutaneous, intraepithelial, sublingual immunotherapy

Allergen immunotherapy (AIT) was first described over a century ago and has continued as a mainstay in the treatment of allergic diseases, such as allergic rhinitis, asthma, and venom allergy.^{1,2} In this review we will discuss the rationale behind using novel immunotherapy approaches for the management of allergic diseases. We will focus on those studies that are in human clinical trials and examine the therapeutic effects noted thus far.

It is important to note the purpose of new immunotherapies to understand the rationale behind their development. Ultimately, the intent of new immunotherapies is to provide better therapeutic options for patients by reprogramming the immune system to ignore insignificant threats without compromising its ability to respond to real threats. Effective immunotherapy should change a person's allergen-specific response from an allergic profile (T_H2) to a nonallergic profile (T_H1) through regulatory T cells to achieve this goal.³ The regulatory T cells release IL-10, which induces IgG₄ and TGF-β, increasing IgA levels.

From ^athe Division of Allergy/Immunology, University of South Florida, Tampa, and ^bthe Division of Allergy/Immunology, Creighton University, Omaha.

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Corresponding author: Thomas B. Casale, MD, Division of Allergy/Immunology, University of South Florida, 12901 Bruce B. Downs Blvd, MDC Bldg, 3rd Floor, Rm 3127, Tampa, FL 33612. E-mail: tbcasale@health.usf.edu. 0091-6749/\$36.00

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Abbreviations used

AIT: Allergen immunotherapy
ILIT: Intralymphatic immunotherapy
MATA: Modified allergen tyrosine absorbate
MPL: Monophosphoryl lipid A
OIT: Oral immunotherapy
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
TLR: Toll-like receptor

Conventional subcutaneous immunotherapy (SCIT) requires 30 to 80 injections with high-dose allergen over 3 to 5 years. This is very time consuming and associated with allergic side effects, including anaphylaxis. Sublingual immunotherapy (SLIT) is more patient friendly (less severe side effects, no injection, and can be done at home), but the treatment duration is still long (several years) and typically requires daily dosing. Because of these disadvantages, it is estimated that less than 5% of all allergic patients who could conceivably be candidates for allergy immunotherapy actually undergo this treatment. Thus there is clearly a need for allergy immunotherapy that is more convenient, effective, and safer. In 2011, we wrote a review for the *Journal of Allergy and Clinical Immunology* describing potential future allergy immunotherapy treatments.⁴ Since that time, there has been considerable progress in allergen extract modifications and additions to standard extracts (Fig 1). Subcutaneous administration is the current norm, but the future holds promise for other options, including SLIT and oral immunotherapy (OIT; Fig 2). Below we describe some of these strategies to improve traditional subcutaneous AIT.

OMALIZUMAB PLUS SCIT

The safety and efficacy of standard SCIT preparations can be improved with the addition of anti-IgE therapy or adjuvants. The use of anti-IgE antibody therapy (omalizumab) in addition to conventional SCIT has been evaluated in several trials. Omalizumab therapy alone decreases serum IgE levels and FcεRI receptor expression on mast cells, basophils, and dendritic cells.⁵ The use of omalizumab before starting AIT improved the safety of SCIT by reducing systemic allergic reactions up to 5-fold, as did the use of epinephrine and prednisone in treating immunotherapy-induced anaphylaxis in patients with allergic rhinitis.⁶ Pretreatment with omalizumab reduced systemic allergic reactions to cluster SCIT by 50% in asthmatic patients.⁷ In addition to increased safety, allergic rhinitis symptoms were reduced in patients treated with a combination of omalizumab and SCIT compared with those treated with SCIT alone.^{6,8,9} A more recent randomized, double-blind, placebo-controlled, multicenter trial used omalizumab or placebo in combination with standard SCIT (depigmented allergoid vaccine) for grass allergy.¹⁰ The core study consisted of a 2-week run-in phase, a preseasonal 10-week treatment phase, and an 8-week seasonal maintenance treatment phase. During follow-up, all patients were treated with the depigmented allergoid vaccine (Depigoid; Laboratorios LETI SL, Tres Cantos, Spain) only over the 2 subsequent years in 4-week intervals. During the first season, the combination of omalizumab plus SCIT reduced symptoms of both asthma and allergic rhinitis to a greater extent. However,

the reduction of asthma and allergic rhinitis symptoms was not noted in subsequent seasons when patients were maintained on SCIT alone.

This approach has also been studied for food allergy. Eleven children with cow's milk allergy received 9 weeks of omalizumab and then underwent oral cow's milk desensitization.¹¹ Double-blind, placebo-controlled food challenges done 8 weeks after omalizumab were discontinued and showed that all 9 patients who reached a daily dose of 2000 mg tolerated more than 8000 mg/d.

Finally, there are case reports of omalizumab plus venom immunotherapy, but the data are limited, and most, but not all, reports favor improved safety with venom immunotherapy when using omalizumab as a pretreatment.

Taken together, these data suggest that pretreatment with omalizumab can add efficacy and safety to immunotherapy administered subcutaneously and orally. It is unclear how long one needs to treat with both therapies and whether one can stop omalizumab and still have improved safety and efficacy. Indeed, the study by Kopp et al¹⁰ suggests the combination might need to continue for a prolonged period to see added therapeutic benefits.

ADJUVANTS

Aluminum salts (alums), such as aluminum hydroxide, are the most widely used adjuvants in SCIT worldwide. The proposed mechanism involves slower release of allergen from the injection site, increasing the duration of antigen presentation. The use of alum-based grass AIT has demonstrated improvements in symptoms and reductions in medication use, but no head-to-head comparisons with non-alum-based AIT have been performed.^{12,13} In addition to aeroallergens, venom immunotherapy with alum-based extracts has been effective.¹⁴ The most common adverse event with alum-based immunotherapy is increased discomfort at the injection site compared with non-alum-based preparations.

Toll-like receptors (TLRs) are innate immune receptors designed to induce regulatory T-cell responses in response to specific pathogens. The addition of TLR agonists to immunotherapy or their use by themselves has shown some benefits.

Monophosphoryl lipid A (MPL) is a detoxified derivative from *Salmonella* LPS that acts as a TLR4 agonist. Pollinex Quattro (Allergy Therapeutics, Worthing, West Sussex, United Kingdom) is a short pollen extract allergoid adsorbed onto L-tyrosine with the addition of MPL (modified allergen tyrosine absorbate [MATA] with MPL).¹⁵ MATA MPL has been shown to reduce symptoms and medication use, increase allergen-specific IgG levels, and blunt seasonal increases in IgE levels. A large randomized, double-blind, placebo-controlled study evaluated more than 1000 patients with 4 preseason injections of MATA MPL grass immunotherapy.¹⁶ During the peak grass season, patients treated with Pollinex had decreased symptom and medicine scores compared with those seen in the placebo group. Treatment seemed more effective for patients with more severe symptoms, those with symptoms for 35 years or more, and those in areas of high grass pollen counts. The concept of only having to administer 4 preseasonal injections is very attractive. US trials have been positive for a number of seasonal allergens, and phase III efficacy studies are underway.¹⁷ MATA MPL is currently available for use in Europe.

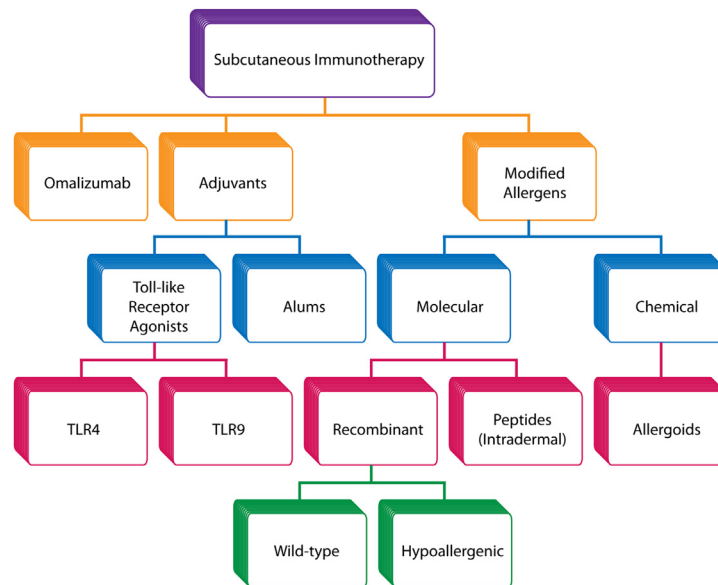


FIG 1. New Strategies for SCIT.

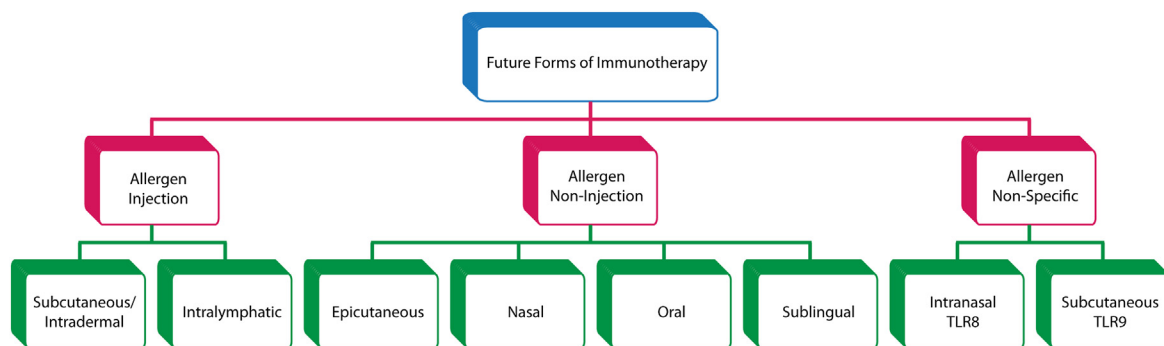


FIG 2. Overview of new immunotherapies in clinical studies.

An early-phase, double-blind, placebo-controlled study with a SLIT formulation of varying concentrations of grass extract and MPL was evaluated in 80 patients with allergic rhinitis.¹⁸ Patients received daily treatments for 8 weeks. Patients treated with the highest MPL amount had reduced nasal challenge responses compared with those seen in the placebo group.

A TLR8 agonist could have a theoretic advantage by directly stimulating myeloid dendritic cells and monocytes. Weekly administration of a nose spray containing a TLR8 agonist for a total of 4 administrations followed by a grass allergen challenge in an exposure chamber showed significant improvements in the actively treated patients.¹⁹ The theoretic advantage of this approach would be that one could treat patients regardless of the source of their allergies without having to spray allergen directly into the nose, thereby possibly avoiding local adverse effects.

TLR9 responds to unmethylated CpG sequences on bacterial DNA. Early studies with ragweed antigen (Amb a 1) bonded to CpG demonstrated less rhinitis symptoms during initial and subsequent ragweed seasons and suppression of a seasonal increase in ragweed-specific IgE levels.²⁰ A subsequent larger multicenter trial did not find significant changes in symptom

scores from baseline in the placebo and treatment groups. Thus no meaningful data could be obtained, and further studies were not undertaken.²¹

More recent studies evaluated the use of a virus-like particle to protect the CpG component (CYT003-QbG10) from degradation. Nearly 300 patients with dust mite allergy were treated with 2 doses of CYT003-QbG10 (without allergen) or placebo injections weekly for 6 weeks.²² Patients receiving the high-dose therapy had significantly less rhinoconjunctivitis symptoms and improved quality-of-life scores. In addition, the conjunctival provocation dose was increased 10-fold in the high-dose CYT003-QbG10 group. A proof-of-concept, parallel-group, double-blind, randomized study published in the *Journal* in 2013 demonstrated that CYT003-QbG10 administered subcutaneously improved many asthma outcomes.²³ In this study asthmatic patients underwent a steroid stabilization phase and then were administered active treatment at weeks 0, 1, 2, 4, 6, 8, and 10. After the fourth week of treatment, patients underwent a 50% reduction in inhaled corticosteroid dose, followed by a 100% reduction as tolerated. The authors found that the active treatment led to improved symptom medication scores over those seen in the placebo group, and this was especially evident during the corticosteroid

reduction phases. Similar results were found with pulmonary function values and asthma quality-of-life indices. The treatment was well controlled, with the majority of adverse events reported as local injection-site reactions. These data suggest that this treatment has steroid-sparing effects in that two thirds of actively treated patients had well-controlled asthma despite steroid withdrawal. An obvious advantage is that this therapy works through an allergen-independent mechanism so that it would not matter to what one was allergic. Large-scale studies are ongoing.

MODIFIED EXTRACTS

Altering allergens is one way to improve the efficacy and safety of AIT. Several methods have been studied. Altering the allergens with formaldehyde or glutaraldehyde produces allergoids, reducing allergenicity while preserving immunogenicity. Purifying the allergen with the known molecular, immunologic, and biological characteristics of the allergen produces wild-type recombinant allergens, whereas altering the structure produces hypoallergenic allergens. Although using just the peptide fragments of the allergen preserves immunologic tolerance, it decreases the propensity for allergic reactions.

Allergoids

Allergoids are commonly used in European SCIT, but there are no current US Food and Drug Administration–approved products in the United States. As previously described, MATA MPL is a combination of an allergoid compound with TLR4 agonist.¹⁵ Allergovit (Allergopharma KG, Reinbek, Germany) is an aluminum hydroxide–adsorbed allergoid preparation of 6 grass pollen allergens. Acaroid (Allergopharma KG) is a dust mite allergoid combined with alum, and Depigoid (Laboratorios LETI SL) is another alum-based allergoid. These allergoids have demonstrated improvement in symptom and medication scores in patients with allergic rhinitis, as well as reduction in inhaled corticosteroid dose in asthmatic patients.^{24–26}

Recombinant vaccines

Recombinant allergen trials have evaluated several different versions of AIT. Wild-type allergens correspond to the natural allergens and are generally equivalent in structure and immunologic properties. Hypoallergenic recombinant allergens are similar to wild-type allergens but with conformational changes in their IgE epitopes reducing their allergenicity. Another method of producing hypoallergenic extracts involves using fragments of the allergenic protein or relevant peptides.

The wild-type recombinant allergens initially studied were birch and grass. Patients treated with recombinant allergens noted decreased rhinitis symptoms with concurrent increased levels of allergen-specific IgG or IgG₁ and IgG₄.^{27,28}

A recent study evaluated a recombinant birch extract that was folded to reduce allergenicity.²⁹ This environmental exposure study with 36 patients with birch tree–induced allergic rhinitis found that 10 weekly injections significantly improved symptoms and increased allergen-specific IgG₁ levels, with grade II adverse reactions noted with the 2 higher doses of extract of the 4 doses evaluated.

The use of birch pollen fragments initially demonstrated typical changes seen in conventional AIT with increased

allergen-specific IgG levels and decreased skin test reactivity, but a double-blind, placebo-controlled trial did not find any significant improvement in symptoms or medication use.^{30–32}

Peptides

Peptide immunotherapy could have some distinct advantages. Vaccines using peptides with T-cell epitopes could induce regulatory T cells and blunt allergic responses. There should be better safety because of the peptides being too small to cross-link IgE on mast cells. Final products have been described as room temperature–stable lyophilized products containing a mix of peptides for injection.

Previous peptide immunotherapy trials were encouraging for cat and bee allergy. More recent studies attempt to improve on the peptide components. A newer version of cat peptide immunotherapy (Cat-PAD) reduced the number of peptides (from 27 in early studies to 7) and added thioglycerol to prevent cross-linking of IgE.³³ In this phase IIa clinical trial of cat peptide immunotherapy, 1 intradermal dose was well tolerated. A follow up randomized, double-blind, placebo-controlled, parallel-group environmental exposure chamber trial evaluated 2 regimens of Cat-PAD peptide immunotherapy in 202 patients with cat allergy.³⁴ Patients received 6 nanomolar Cat-PAD injections every 4 weeks for a total of 4 injections. They subsequently were placed in an environmental exposure chamber on 4 successive days to determine whether active treatment inhibited allergic rhinoconjunctivitis symptoms. They found inhibition in the first year of treatment, but more interestingly, patients who received active treatment had sustained inhibition to allergen challenge 1 year after the 4 injections. These data suggested peptides manufactured synthetically could allow an easier course of immunotherapy without requiring dose escalation and perhaps therapeutic benefits for up to a year. The use of Fel d 1 peptides fused with the hepatitis B PreS domain is currently being studied and might be 1000 times less allergenic with maintained immunogenicity.³⁵ Further studies are ongoing to determine the appropriate dosing regimen and duration of effect of peptide immunotherapy.

ALTERNATIVE METHODS OF DELIVERY

Alternative strategies for better AIT include the use of local (target organ) immunotherapy, the administration of AIT to facilitate enhanced uptake of the allergen by key immune effector cells (epicutaneous and intralymphatic), and the use of OIT/SLIT to improve on the safety of SCIT.

Nasal immunotherapy

Local nasal immunotherapy was described more than 20 years ago. In a study by Marcucci et al,³⁶ dry powder or a solution of allergens was sprayed into the nose during vocalization. In their local nasal immunotherapy study involving 32 children with dust mite–induced allergic rhinitis, they found that children in the active treatment group showed significant improvements in rhinitis symptoms and a reduction in drug consumption and allergen-specific nasal reactivity after 18 months. No major local or systemic side effects were observed in the children who completed the study, but local adverse events were common.

More recently, a new approach has been tried with local nasal immunotherapy using dust mite-coated strips placed in the nose.³⁷ The authors speculated that this would be a better alternative by reducing nasal reactions and avoiding the difficult application needed by dry powder or solution administration. Patients with dust mite-induced allergic rhinitis were recruited to receive 4 months of local nasal immunotherapy. Patients were instructed to place the dust mite-coated strips on the nasal septum for 10 minutes every week for 4 months. The authors found that active treatment resulted in a decrease in sneezing, rhinorrhea, and nasal stuffiness in comparison with placebo. Although better tolerated, some patients had persistent nasal responses after strip application. These data suggest that use of local nasal immunotherapy might provide some therapeutic benefit. However, the local adverse effects might be problematic for some patients.

Epicutaneous immunotherapy

Because there are high numbers of antigen-presenting cells in the skin, investigators have also looked to enhance the efficacy and shorten the treatment duration of AIT by means of epicutaneous administration. An early study used grass allergen on a patch applied to the forearm. Patients were treated for 48 hours at weekly intervals for a month during the grass season.³⁸ During that season and the next grass season a year later, patients treated with grass allergen had significantly less rhinitis symptoms compared with the placebo patch-treated patients. Increased eczematous lesions were noted with the allergen patches compared with placebo patches.

A follow-up phase II, double-blind, placebo-controlled study to evaluate optimal dosing included 132 patients with grass-induced allergic rhinitis.³⁹ Those patients receiving the highest patch allergen concentration (approximately 30 µg of grass antigen) noted improvement in rhinitis symptoms compared with placebo-treated patients of 32% during the initial treatment year and of 24% the following year. Local side effects were common from the grass patches, and systemic reactions were noted in 8% of all patients (1 with placebo and 10 with allergen extract). All reactions responded to corticosteroids and antihistamines, and none required epinephrine. The dropout rate because of adverse events was 8.3%. A pilot study evaluated epicutaneous immunotherapy to cow's milk protein by using a new topical delivery system (Viaskin; DBV Technologies SA, Paris, France).⁴⁰ In this small 90-day trial, the cumulative tolerated milk dose did not significantly differ between the active treatment and placebo groups, but there was a trend toward improvement. Local reactions at the site (erythema, eczema, and pruritis) were twice as common in the active group, but adverse reactions were mild. Thus although possibly effective, more work is needed to accurately determine the best therapeutic and safety regimens for epicutaneous treatment.

Intralymphatic immunotherapy

Intralymphatic immunotherapy (ILIT) uses lower doses of antigen than typical because of the enhanced delivery to key immune cells. In this approach inguinal lymph nodes are first identified by using small ultrasound probes, and the immunotherapy is injected into the nodes, with discomfort reported to be similar to that accompanying venous puncture. An initial study in 2008 demonstrated that 3 low-dose grass extract inguinal lymph

node injections were equivalent to 3 years of standard SCIT in relieving rhinitis symptoms and inducing tolerance.⁴¹ Systemic reactions were less in the ILIT-treated patients (6 mild) compared with the SCIT-treated patients (18 mild and 2 severe).

In a study published in the *Journal* in 2012, investigators used recombinant Fel d 1 fused to the HIV-derived translocation peptide transactivator of transcription to enhance cytoplasmic uptake.⁴² A truncated human invariant chain was also fused to Fel d 1 to increase presentation through the MHCII pathway. This resulted in a modular antigen transporter vaccine, which was placed in alum and compared with saline in alum. Twelve active-treated and 8 placebo-treated patients received intralymphatic injections every 28 days for 3 doses. Therapy with cat ILIT improved nasal challenge tolerance by 74-fold, whereas placebo-treated patients had an improvement of less than 3-fold. Five weeks after the final treatment, they found a significant increase in cat-specific IgG₄ levels. The effects of this treatment were studied 300 days later, but only 13 patients remained. Nonetheless, there was a small trend for continued improvement in symptoms.

Another pilot study with alum-based birch or grass found improvement in symptoms equivalent to standard SCIT for 3 years with a similar discomfort profile.⁴³ This small (15 patients) randomized, placebo-controlled study demonstrated decreased nasal inflammation and was well tolerated. Recent studies with bee venom ILIT demonstrated protection from bee stings in a small proof-of-concept study, but a larger multicenter trial was discontinued because of increased adverse events.⁴⁴ The first randomized, double-blind, placebo-controlled study in 43 patients using 2 dosing regimens of grass ILIT found no improvement in combined symptom-medication scores compared with those seen in the placebo group, despite increases in IgG₄ levels.⁴⁵ Patients treated with active grass ILIT commonly (83%) had local swelling. Overall, these data suggest that a small number of ILIT injections with lower doses of antigen might prove to be an effective therapeutic modality, but much work needs to be done to define the optimal therapeutic regimen.

OIT

OIT has continued to advance the quest for food allergy treatment. Early small trials have demonstrated the benefits of milk, egg, and peanut OIT.⁴ A 2012 Cochrane meta-analysis evaluated 196 patients in 5 trials of cow's milk OIT.⁴⁶ Of those patients treated with milk OIT, 62% could ingest a full serving of milk, and 27% could ingest a partial serving, whereas in the control group only 8% tolerated a full serving, and none tolerated a partial serving. Local and mild adverse reactions were common in the milk treatment groups.

A recent review of 6 studies of peanut OIT concluded that peanut OIT increases the threshold peanut dose with minor adverse reactions, although some were potentially more serious.⁴⁷ The authors believed that because of this risk, OIT should not be used outside clinical trials at this point in time.

A recent double-blind, placebo-controlled study on 28 children with peanut allergy evaluated the effectiveness and safety of a year of OIT.⁴⁸ In fact, this was the only study that fulfilled qualifications for a Cochrane meta-analysis review.⁴⁹ After a year of treatment with peanut protein or placebo, children treated with active therapy were able to tolerate the maximum dose of

TABLE I. Novel immunotherapy

Administration route	Allergens	Adjuvant	Modification
Subcutaneous	Inhalant allergens	Omalizumab	Allergoid
Subcutaneous	Inhalant allergens	Alum	
Subcutaneous	Inhalant allergens	TLR4 agonist (SLIT formulation)	Allergoid
Subcutaneous	Inhalant allergens/ no allergen	TLR9 agonist plus allergen or alone	
Subcutaneous	Inhalant allergens		Wild-type recombinant
Subcutaneous	Inhalant allergens		Hypoallergenic recombinant
Subcutaneous	Inhalant allergens		Allergoid
Subcutaneous/ intradermal	Inhalant allergens and venom		Peptides
Intralymphatic	Inhalant allergens and venom	Alum	Recombinant
Intranasal	Inhalant allergens		
Intranasal	Inhalant allergens/ no allergen	TLR8 agonist alone	
Epicutaneous	Inhalant allergens		
Oral	Food		(Baked)
Sublingual	Inhalant allergens and food		

5000 mg (20 peanuts), whereas placebo-treated patients had a median threshold dose of 280 mg, and none were able to tolerate the maximum dose. Immunologic changes noted with patients receiving active treatment mirrored the changes noted in natural tolerance, including increases in regulatory T-lymphocyte numbers and peanut-specific IgG and IgG₄ levels, a transient increase in peanut-specific IgE levels, and a decrease in peanut skin prick test responses. Of note, 3 (16%) of the 19 patients receiving active treatment were unable to complete the protocol because of adverse reactions.

A double-blind, placebo-controlled study evaluated 55 children with egg allergy treated with OIT or placebo for 10 months and continued children on active egg therapy for a total of 22 months.⁵⁰ At 10 and 22 months, none of the placebo-treated patients passed the oral challenge, whereas 55% of the children receiving active OIT passed at 10 months, 75% at 22 months, and 28% at 24 months (2 months after therapy ended). Those children who passed the oral challenge at 24 months had decreased skin prick test responses to egg and increased egg-specific IgG₄ levels and were able to eat eggs a year after study completion without any symptoms.

An alternative to standard OIT is baked food ingestion. The ingestion of baked food (egg or milk) daily improves oral tolerance. Moreover, patients are able to tolerate the unheated food at an earlier timeframe than those not ingesting baked allergen daily.^{51,52}

Unanswered questions with OIT for foods concern the length of treatment and the duration of improvement. When previous milk OIT-treated patients were evaluated 3 to 4 years after OIT completion, symptoms commonly returned, with only 31% asymptomatic or minimally symptomatic with full cow's milk servings.⁵³

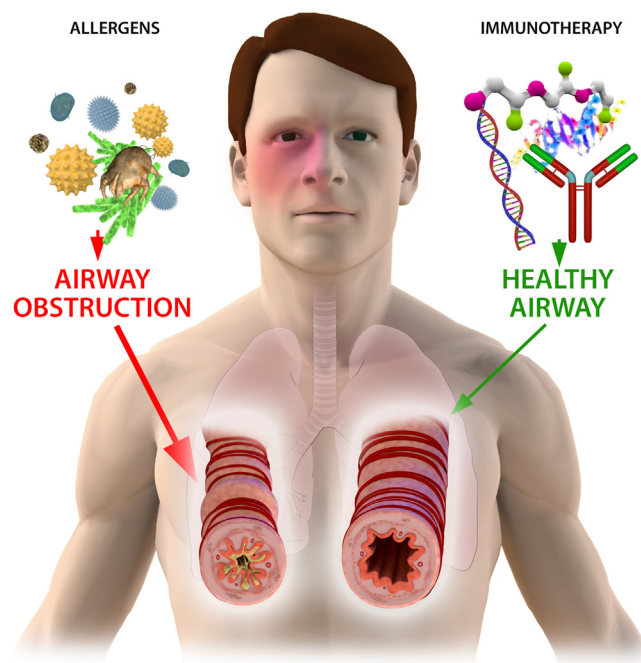


FIG 3. Effects of AIT on allergen-induced airway inflammation. Many novel forms of AIT hold promise to relieve allergic airway inflammation, leading to healthier airways and decreased symptoms.

SLIT

SLIT requires the allergen extract (either as liquid or dissolvable tablet) to be held under the tongue to allow absorption. Since our last review, several meta-analyses have evaluated the effectiveness of SLIT for allergic diseases. In 2011, Radulovic et al⁵⁴ updated their previous Cochrane meta-analysis reviewing 49 suitable studies with 4500 patients and found a significant reduction in symptoms and medication use for SLIT compared with placebo. In 2010, Di Bona et al⁵⁵ reviewed 19 studies with nearly 3000 patients treated with grass SLIT and found SLIT significantly reduced both rhinitis symptoms and medication use. Adults seemed to respond better to therapy than children, and those treated for more than 12 weeks had improved outcomes. Looking at only allergic conjunctivitis, another meta-analysis of 42 studies and nearly 4000 patients concluded SLIT was effective in reducing total and individual eye symptoms compared with placebo, whereas eye drop medication use was unaffected.⁵⁶ The most recent published meta-analysis in 2013 found strong evidence supporting the use of SLIT in improving asthma symptoms and moderate evidence of decreased rhinitis and conjunctivitis symptoms and medication use in conjunctivitis, rhinitis, and asthma.⁵⁷ After treatment with SLIT for 4 to 5 years, sustained benefits have been observed for 7 to 12 years.⁵⁸ In 2013, the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology consensus report concluded that both SCIT and SLIT can prevent development of asthma and new sensitizations.⁵⁹ Mild gastrointestinal and oral pruritus side effects are common with aeroallergen SLIT.

It is unclear whether SCIT or SLIT has better outcomes. SCIT seems to be more effective than SLIT in reducing symptoms for dust mite and grass allergy.^{60,61} A recent review could not find conclusive evidence of superiority of SLIT or SCIT because of

a lack of true head-to-head studies, but the trend favored SCIT as the more effective therapy.⁶²

Most studies with SLIT involve monotherapy, even though many patients in Europe have polysensitization. Evidence suggests that those patients still benefit from SLIT monotherapy to the same extent as monosensitized patients.⁶³

Several researchers have studied the use of SLIT for food allergy (peanut, milk and hazelnut) and found SLIT to be effective in desensitization to food allergy, although likely not as effective as OIT.⁶⁴⁻⁶⁸

CONCLUSION

This is an exciting time for allergists/immunologists engaged in the practice of allergy immunotherapy. Many novel and likely better therapeutic options are under development (Table I). Ultimately, therapies that decrease symptoms and improve quality of life with sustained immunomodulation and a favorable risk/benefit ratio are the desired end products (Fig 3).

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