

Clinical reviews in allergy and immunology

Future forms of immunotherapy

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Allergic respiratory diseases affect approximately 15% of the US population. Allergen immunotherapy has been a treatment option for diseases such as allergic rhinitis, allergic asthma, and venom allergy for the last 100 years. During the first 75 years, conventional subcutaneous immunotherapy did not change much. However, the last 25 years has seen substantial growth in the development of alternatives to conventional subcutaneous immunotherapy. The addition of omalizumab, an anti-IgE mAb, to immunotherapy offers the potential for increased safety and efficacy. Activation of the innate immune system through Toll-like receptor agonists with and without specific allergens appears to improve the immunologic responses and clinical outcomes in patients with allergic diseases. The use of chemically altered allergens, allergoids, recombinant allergens, and relevant T-cell epitope peptides are all approaches that have yielded positive results. Finally, alternative modes of delivery hold promise, with sublingual immunotherapy rapidly approaching mainstream use in many countries. One thing is clear: the next century of immunotherapy will be vastly different from today's current standard of care. (*J Allergy Clin Immunol* 2010;■■■:■■■-■■■.)

Key words: Immunotherapy, allergy, asthma, omalizumab, allergens

Allergic diseases have increased in prevalence over the last 20 years, affecting as many as 40 to 50 million persons in the United States. Allergen immunotherapy has been a treatment option for allergic disease since it was first introduced by Noon¹ and Freeman² nearly a century ago. Allergen immunotherapy alters the course of allergic diseases, thereby reducing symptoms and medication use. A recent meta-analysis of 51 studies with 2871 patients with allergic rhinitis demonstrated a reduction in symptoms by 73% and medication use by 57% with subcutaneous immunotherapy (SCIT).³ In addition to allergic rhinitis, multiple placebo-controlled trials have demonstrated the effectiveness of SCIT in allergic asthma and stinging insect allergy. For venom allergy, successful completion of SCIT can be considered curative.

Abbreviations used

AIC: Amb a 1-immunostimulatory conjugate
HDM: House dust mite
ISS: Immunostimulatory sequence
PLA2: Phospholipase A₂
SCIT: Subcutaneous immunotherapy
SLIT: Sublingual immunotherapy
TLR: Toll-like receptor
VLP: Virus-like particle

Other benefits of SCIT include the prevention of new sensitizations and the decreased risk of asthma in patients with allergic rhinitis.^{4,5}

The mechanism of action of allergen immunotherapy involves shifting a patient's immune response to a specific allergen from a predominately allergic T-lymphocyte (T_H2) response to a "nonallergic" T-lymphocyte (T_H1) response while inducing regulatory T lymphocytes (Fig 1).⁶ Regulatory T cells downregulate allergic immune responses in part through the release of IL-10 and TGF- β . IL-10 causes a shift from allergen-specific IgE to allergen-specific IgG4, whereas TGF- β increases allergen-specific IgA levels. With allergen immunotherapy, the seasonal increase in allergen-specific IgE levels is blunted, whereas protective allergen-specific IgG4 production is increased.

Despite the benefits of SCIT, not everyone improves, and patients are at risk of anaphylaxis caused by allergen immunotherapy. Thus there is a need for safer and more effective allergen immunotherapy strategies, especially for patients with asthma. Newer forms of allergen immunotherapy are designed to lessen T_H2 responses to allergens and provide a safer alternative to SCIT. This might involve adding therapy to standard SCIT, altering the allergen extract, or changing the mode of delivery of the allergen extract (Fig 2).

SCIT PLUS OMALIZUMAB

One therapeutic option is the addition of the immunomodulating agent omalizumab, an anti-IgE recombinant humanized mAb approved for use in patients with moderate-to-severe perennial allergic asthma, to SCIT. Omalizumab preceding allergen immunotherapy should provide greater safety by reducing serum IgE and Fc ϵ R1 receptors on dendritic cells, mast cells, and basophils. In a double-blind, parallel-group, placebo-controlled trial adults with allergic rhinitis were randomized to either 9 weeks of omalizumab or placebo, followed by 1-day rush or placebo ragweed immunotherapy and then 12 weeks of omalizumab or placebo plus ragweed immunotherapy.⁷ Omalizumab had a protective effect on allergic-type reactions caused by both rush and maintenance immunotherapy. Omalizumab reduced allergic reactions, including anaphylactic reactions, 5-fold and decreased the use of epinephrine and prednisone to treat anaphylaxis. In

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Disclosure of potential conflict of interest: T. B. Casale is on the Stallergenes advisory board; has received research support from Novartis, Genentech, Stallergenes, and Schering-Plough; and is Executive Vice President of the American Academy of Allergy, Asthma & Immunology. J. R. Stokes has received speaker's honoraria from the Advancing Respiratory Care Network subset of the Respiratory Allergic Disease Foundation and has received research support from Novartis, Genentech, Stallergenes, and Schering-Plough.

Received for publication September 21, 2010; revised October 19, 2010; accepted for publication October 19, 2010.

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0091-6749/\$36.00

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doi:10.1016/j.jaci.2010.10.034

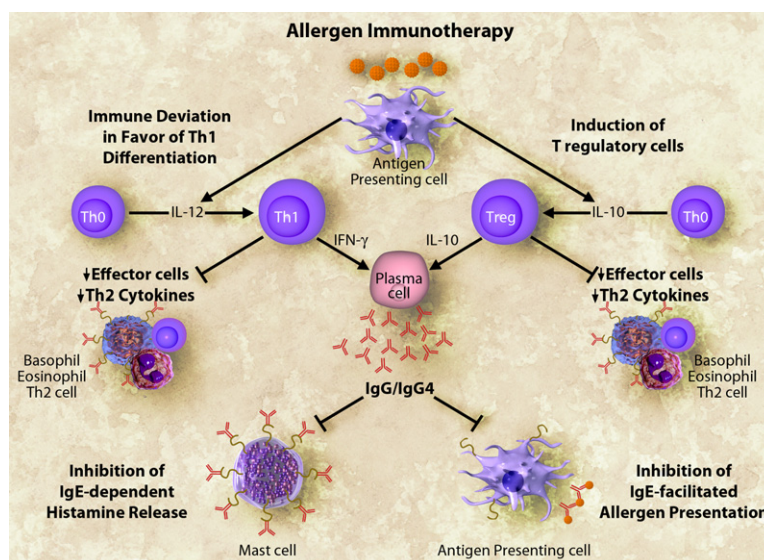


FIG 1. Putative mechanisms of allergen immunotherapy.

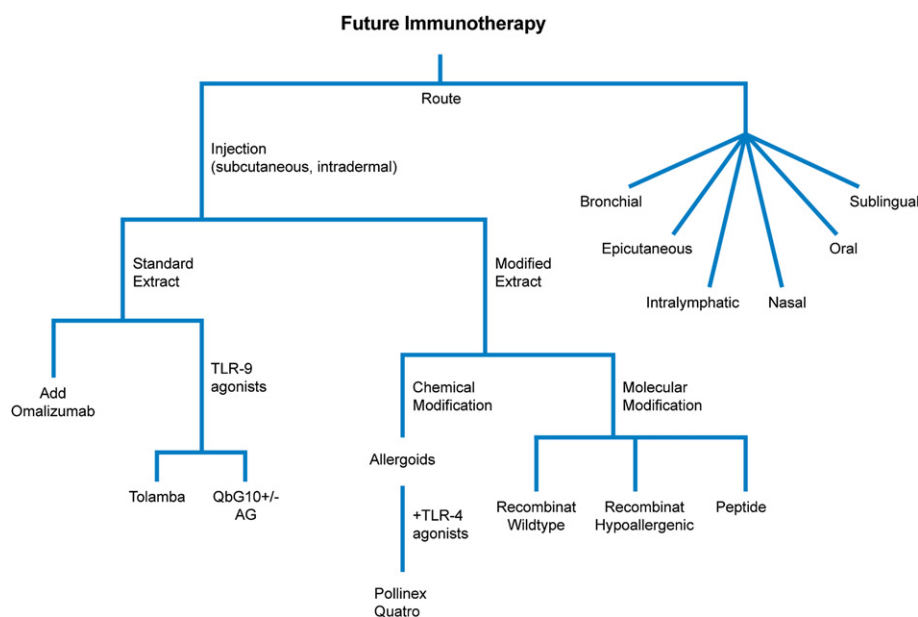


FIG 2. Future potential immunotherapy treatments in clinical development.

addition, the omalizumab plus SCIT arm had less allergic rhinitis symptoms than the SCIT-only group. In children with allergic rhinitis, the addition of omalizumab to maintenance SCIT was more effective in reducing allergic rhinitis symptoms than SCIT alone.⁸

Patients with unstable asthma are at a greater risk of systemic, potentially life-threatening reactions to allergen immunotherapy. A multicenter, double-blind, parallel-group study of adult patients with moderate persistent uncontrolled asthma receiving inhaled corticosteroids underwent treatment with either omalizumab or placebo for 12 weeks before a 4-week, 18-injection cluster SCIT regimen, which was followed by 7 weeks of maintenance allergen immunotherapy to perennial allergens.⁹ Pretreatment with omalizumab significantly reduced total systemic allergic reactions from SCIT, and patients had fewer severe reactions. In addition, a significantly higher proportion of patients

receiving omalizumab were able to reach the target maintenance dose of allergen immunotherapy.

These data indicate that omalizumab pretreatment of patients undergoing SCIT confers additional safety to SCIT and added efficacy for symptom control. It remains to be determined whether these positive effects persist if the omalizumab is discontinued while the SCIT is continued for 3 to 5 years. Thus far, the studies have been too short term to address this important issue. Also, it is unclear what immunologic mechanisms are responsible for the added efficacy.

TOLL-LIKE RECEPTORS

Toll-like receptors (TLRs) are innate immune receptors designed to respond to a variety of pathogens and induce T_H1

and regulatory T-cell responses.¹⁰ Endotoxins, such as LPSs, are agonists for TLR-4 receptors.¹¹ TLR9 responds to nucleotide sequences of unmethylated CpGs, which are common in bacterial DNA but are suppressed and methylated in eukaryotic DNA. There have been a variety of strategies using these TLR agonists to improve traditional SCIT.

Pollinex Quattro (Allergy Therapeutics, West Sussex, United Kingdom) is a short pollen extract that is chemically modified by glutaraldehyde and adsorbed onto L-tyrosine with the addition of the TLR-4 agonist monophosphoryl lipid A. Therapeutic trials have been conducted in both pediatric and adult patients with allergic rhinitis, allergic conjunctivitis, and asthma to grasses, trees, or ragweed.^{12,13} Pollinex Quattro is administered as a pre-seasonal course of 4 injections over at least 3 weeks annually. Therapy has been shown to significantly reduce skin prick test reactions and the seasonal allergen-induced increase in IgE levels while increasing allergen-specific IgG levels.¹³ In a postmarketing survey of more than 3000 patients given 21,428 injections over 3 years, allergic rhinitis symptoms improved in 93% of patients, and medication use decreased in 75%. Local reactions occurred after 6.3% of injections and systemic reactions occurred after 0.5% (mainly rhinitis symptoms), with no serious or anaphylactic reactions reported.¹⁴ Similar results were seen in a pediatric population of more than 400 patients, with response to treatment assessed as good or very good in 94% of patients. Rescue medication use decreased from 83% to 24% after the first treatment course and to 13% after the second course.¹⁵ Early trials in the United States have demonstrated positive results for both grass and ragweed but have been temporarily suspended because of an adverse event and the ensuing evaluation as to causality.

Early studies with inhaled CpG immunostimulatory sequences (ISSs) on allergen-induced airway responses altered the T_H1 profile by stimulating expression of IFN- γ and interferon-inducible genes.¹⁶ However, there was no effect on allergen-induced early or late decreases in FEV₁ compared with placebo, nor was there a reduction in allergen-induced sputum eosinophil numbers or T_H2-related gene expression.¹⁶

Covalently bonding an ISS with an allergen, such as ragweed antigen (Amb a 1), dramatically enhanced the ability of ISSs to modify antibody and T-cell responses to the allergen by reducing allergenicity and improving immunogenicity, especially T_H1 responses.^{17,18} *In vitro* studies with CpG ISSs in combination with Amb a 1 reversed the ragweed-induced T_H2 profile, with decreased IL-5 secretion and increased IFN- γ production from PBMCs.¹⁹ A follow-up *in vivo* study demonstrated that ragweed-induced T_H2 responses were shifted toward T_H1 responses, with significant increases in IFN- γ levels.²⁰ In an early clinical study, ragweed-sensitive patients with allergic rhinitis received 6 escalating doses of Amb a 1-immunostimulatory conjugate (AIC; trade name TOLAMBA; Dynavax Technologies, Berkeley, Calif) or placebo before the ragweed season.²¹ Patients treated with the conjugate had a significantly reduced increase in eosinophil and IL-4 mRNA-positive cell numbers and an increased number of IFN- γ mRNA-positive cells compared with those seen in placebo-treated patients 4 to 5 months later. No symptom improvement was noted after the initial ragweed season, but during the following ragweed season, AIC-treated patients had less chest symptoms and a trend toward less nasal symptoms.²¹ Another phase II study with 6 escalating doses of AIC once weekly before the ragweed season resulted in decreased peak season rhinitis symptoms and medication use during both

the first and subsequent ragweed seasons.²² The seasonal Amb a 1-specific IgE antibody levels were suppressed for both seasons, whereas a transient Amb a 1-specific IgG level increase was noted only during the first season. Immediate skin test reactivity was also decreased in the conjugate-treated patients compared with that seen in the placebo-treated patients. In addition, the ragweed-induced T_H2 cytokine profile was inhibited, and IFN- γ mRNA levels were increased in nasal mucosa after AIC therapy.²³

However, the development of TOLAMBA was discontinued after interim analysis of 716 patients in a large multisite trial demonstrated only minimal ragweed-induced allergic rhinitis symptoms in the placebo group, and as a result, no meaningful efficacy data could be measured. Patients from the Midwest (more than half the study patients) treated with placebo did have greater ragweed symptoms, and the TOLAMBA-treated patients had reduced total nasal symptom scores.²⁴ This illustrates the importance of the proper conduct of studies and the selection of appropriate patients to meet key end points.

Another therapeutic option involves packaging CpG ISSs into virus-like particles (VLPs) to protect them against proteases, decrease adverse reactions, and improve uptake by antigen-presenting cells. Both subcutaneous and intramuscular administration of house dust mite (HDM) allergen extract plus CpG inserted into VLPs markedly increased HDM-specific IgG and IgM levels within 30 days of treatment.²⁵

A phase I/IIa study evaluated subcutaneous injection of CpG ISSs contained in VLPs (CYT003-QbG10) together with HDM allergen for 10 weeks in 20 patients with HDM allergy.²⁶ After treatment with QbG10, skin test reactivity to HDM was reduced, and this effect persisted for up to 38 weeks. The median individual increase in conjunctival allergen provocation dose was 100-fold greater after the treatment, with 1 patient demonstrating a 10,000-fold increase. Within 10 weeks of therapy, patients were nearly symptom free, and the clinical benefit lasted for 38 weeks after treatment. After treatment, allergen-specific IgG levels increased, whereas there was a transient increase in allergen-specific IgE levels. A follow-up randomized, double-blind, placebo-controlled phase II study of patients with mild-to-moderate perennial allergic rhinoconjunctivitis treated weekly for 6 weeks with subcutaneous injections of either CYT003-QbG10 alone (without antigen) or placebo has been completed.²⁷ CYT003-QbG10 led to improvements in both asthma and rhinitis symptoms. A large phase IIb study with 300 patients with perennial rhinitis is underway. In addition, a press release from Cytos (Zurich, Switzerland) indicated that in a 63-patient study CYT003-QbG10 improved symptoms and pulmonary functions in patients with chronic persistent asthma receiving inhaled corticosteroids.

These data suggest that TLR agonists either in combination with allergen or alone might evoke unique immunologic responses that could lead to novel and effective immunotherapy regimens in the future.

ALLERGOIDS

The modification of allergens with glutaraldehyde or formaldehyde produces allergoids, which theoretically reduce IgE epitopes while preserving T-cell epitopes.²⁸ Allergoids are commonly used in European SCIT, but there are no current US Food and Drug Administration–approved products in the United States. Pollinex Quattro is a unique allergoid because of the addition of the TLR-4 agonist monophosphoryl lipid A. Another compound, Allergovit (Allergopharma KG, Reinbek, Germany), is an

aluminum hydroxide-adsorbed depot allergoid preparation of 6 grass pollen allergens. In a 2-year, double-blind, placebo-controlled study in patients with allergic rhinoconjunctivitis, treatment with Allergovit reduced symptom and medication scores, increased grass-specific IgG1 and IgG4 levels, and increased allergen tolerance by means of conjunctival provocation testing.²⁹ Improvements in medication and symptom scores and quality of life continued after a third year of treatment.³⁰ In the pediatric population symptomatic and inflammatory parameter improvement have also been demonstrated with Allergovit. These changes include decreases in seasonal grass-specific IgE level increases and inhibition of the production of IL-4. Skin test and nasal reactivity also decreased in the actively treated patients after 1 year of immunotherapy.

Depogoid (Leti Pharma GmbH, Witten, Germany), an allergoid to tree pollen, improved combined rhinoconjunctivitis symptom and medication scores compared with placebo, with 64% of patients responding to therapy.³¹ In children with asthma, the use of allergoid SCIT to dust mite improved morning peak flows while reducing the inhaled corticosteroid dose compared with placebo.³² One concern is that the low allergenicity of allergoids in comparison with standard extracts might actually be associated with reduced immunogenicity.²⁸ Nonetheless, this remains a promising alternative approach to traditional SCIT, and future studies should be encouraged.

RECOMBINANT ALLERGENS

Recombinant allergens are purified allergens produced by using the allergen's known molecular, immunologic, and biological characteristics. One form is a recombinant wild-type allergen in which the allergen is produced to mimic the properties of the natural allergen. Recombinant allergens can also be produced to reduce allergenic activity, increase immunogenicity, or both.³³

Two studies in 2005 evaluated the use of recombinant wild-type pollen extracts in patients with allergic rhinitis. The first used a mixture of 5 different recombinant allergens of timothy grass in a randomized, double-blind, placebo-controlled study on 62 patients with allergic rhinitis.³⁴ Patients were treated with subcutaneous injections for 18 months. Patients receiving recombinant therapy compared with placebo had a 36% decrease in both symptoms and medication use during the grass season. By the first pollen season, some improvement in quality-of-life scores was present in the patients receiving active treatment, and significant improvements in 5 of 7 domains were shown in the second pollen season. Active treatment led to an increase in grass-specific IgG1 levels and a 4000-fold increase in IgG4 levels, with no change in allergen-specific IgE levels. About 1% of recombinant grass allergen injections led to systemic reactions.³⁴

The second study was a multicenter, randomized, double-blind, placebo-controlled trial comparing recombinant birch pollen allergen vaccine, standard birch pollen extract, natural purified birch pollen allergen, and placebo in 134 patients with birch allergy.³⁵ Patients were treated with subcutaneous injections for 2 years. All 3 actively treated groups demonstrated equal improvements in symptoms, medication use, and skin test reactivity in both pollen seasons compared with those seen in placebo-treated patients. Patients treated with recombinant allergen had a greater increase in Bet v 1 IgG levels and greater decreases in skin test reactivity than either the standard or purified birch extract-treated patients.³⁵

Compared with wild-type recombinant birch pollen extracts, recombinant Bet v 1 fragments or Bet v 1 trimers were 100 times less allergenic by means of skin testing.³⁶ Treatment with Bet v 1 fragments and Bet v 1 trimers in a small group of patients with birch allergy increased nasal secretion of Bet v 1 IgG4 and decreased nasal provocation responses to birch pollen.³⁷ The use of Bet v 1 fragments or Bet v 1 trimers increased allergen-specific IgG1, IgG2, and IgG4 levels to cross-reactive allergens, such as alder pollen, hazel pollen, celery, carrot, and apple. In 7 of 25 actively treated patients (fragments, 5; trimers, 2), there were improvements in oral allergy syndrome symptoms, whereas only 1 of the placebo-treated patients reported improvement. Recombinant Bet v 1 therapy also reduced the seasonal increase in antigen-specific IgE levels a year after therapy.^{38,39} The Bet v 1 trimers retain more of the folded configuration of natural Bet v 1 compared with Bet v 1 fragments, and the trimers increase the production of Bet v 1 IgE more than the fragments.⁴⁰ Therapy with the trimer preparation was associated with more local side effects, whereas the Bet v 1 fragments were more likely to induce systemic reactions. Despite the immunologic changes seen with Bet v 1 trimer and fragment therapy, a double-blind placebo-controlled trial with 124 patients only demonstrated trends toward symptom and medication score improvement.⁴¹

Other techniques to create hypoallergenic extracts include creating point mutations on the IgE binding site to reduce the allergenicity while maintaining the overall allergen structure.⁴² Another procedure involves fusing major allergens, such as bee venom Api m 1 and Api m 2, to delete B-cell epitopes while preserving T-cell epitopes.⁴³ Hypoallergenic tree pollen and dust mite allergens have been produced by means of DNA shuffling to maintain the T-cell epitopes but decrease the allergenicity of the substance.^{44,45}

PEPTIDES

Another strategy involves the use of peptide fragments of corresponding T-cell epitopes of the specific allergens to induce immunologic tolerance and decrease allergenicity. The small size of the peptides reduces their ability to cross-link allergen-specific IgE on mast cells.⁴⁶ Early studies of Fel d 1 peptide therapy used 2 peptides of 27 amino acids in length (Allervax Cat; Circassia, Oxford, United Kingdom). In 95 patients with cat allergy, subcutaneous administration of 3 different doses of peptides occurred weekly for 4 weeks. Only high-dose therapy was effective in reducing nasal and respiratory symptoms after cat room exposure. Side effects consistent with immediate hypersensitivity reactions occurred an hour or more after the first high-dose administration in 16 of 24 patients.⁴⁷ Patients receiving active therapy did have more pruritus, allergic rhinitis symptoms, and asthma symptoms a few hours after dosing.⁴⁸ Patients treated with medium- or high-dose injections of Allervax Cat had improved methacholine challenge responses. The only cytokine change noted was a decrease in IL-4 levels in the high-dose treatment group.⁴⁹ However, decreases in IL-4 levels or other cytokine changes have not been a consistent finding.⁴⁸

A multicenter, randomized, double-blind, placebo-controlled study of 133 patients with cat allergy chronically exposed to cats or who had unsuccessful previous cat immunotherapy were treated with Allervax Cat twice weekly for 2 weeks, which was repeated 4 months later for a total of 8 subcutaneous injections.⁵⁰ All actively treated patients had improvement in the ability to

tolerate cat exposure. Only high-dose peptide-treated patients with decreased baseline lung functions demonstrated a significant improvement in FEV₁ 3 weeks after treatment. Adverse reactions were common for all treatment groups, with 108 patients having at least 1 adverse reaction, but reactions were 20% more frequent in the Allervax Cat treatment group. Severe reactions occurred in 7% of placebo-treated patients and 17% of patients receiving active treatment, with 3 patients in the active treatment group requiring epinephrine.⁵⁰

More recent studies of Fel d 1 peptides administered intradermally used smaller peptides (16-17 amino acids in length) and more peptides (12 vs 2). It was believed that the larger peptides allowed cross-linking of IgE and caused the immediate allergic reactions. With the smaller peptides, late responses still persisted. Peptide therapy provoked isolated late asthmatic reactions in 9 of 40 patients with cat allergy despite no visible early or late cutaneous response. It is postulated that these smaller peptides can directly initiate a T cell-dependent late asthmatic reaction without first invoking an early response dependent on IgE or mast cells.⁵¹ In 8 patients with late asthmatic reactions, the only changes noted 6 hours after administration of Fel d 1 peptides were increases in CD8⁺ cell numbers in the skin and a decrease in IL-5 levels in bronchoalveolar lavage fluids but no changes in bronchial biopsy specimens.⁵² In those patients with late asthmatic responses, reinjection of cat peptide resulted in a marked reduction or complete inhibition of late asthmatic responses that took up to 40 weeks to return. One intradermal dose of Fel d 1 peptides reduced both proliferation of PBMCs and production of IL-4, IL-13, and IFN- γ *in vitro*.⁵³ In a placebo-controlled, double-blind study of 24 patients with asthma and cat allergy, patients were treated with placebo or increasing intradermal doses of Fel d 1 peptides at 3- to 4-day intervals over 2 weeks.⁵⁴ Four of the 16 patients receiving Fel d 1 peptides had initial late asthmatic reactions but tolerated the rest of the doses. In the peptide-treated patients late-phase cutaneous reactions to whole cat dander and Fel d 1 were significantly smaller at follow-up than at baseline. No changes in airway responsiveness or cytokine profile were found with peptide therapy in this study, whereas others have found improvement in histamine PC₂₀ values with peptide treatment.⁵⁴ Skin biopsy specimens demonstrated an increase in T_H1 rather than T regulatory cell numbers at cutaneous late-phase reaction sites.⁵⁵ In a small study of asthmatic patients with cat allergy, Fel d 1 peptide improved asthma quality of life and allergic rhinitis symptoms.⁵⁶

In patients with bee venom allergy, therapy with peptides derived from the major allergens Api m 1 and phospholipase A₂ (PLA₂) has shown promise. In an open study 5 patients with bee venom allergy received a mixture of 3 peptides of PLA₂ at weekly intervals.⁵⁷ After bee sting challenge, 3 of the patients receiving peptide therapy were completely protected, whereas the remaining 2 patients had only mild systemic allergic reactions. After sting challenge, peptide treatment was associated with a marked increase in serum levels of allergen-specific serum IgG4 and IgE. The ratio of PLA₂-specific IgE to IgG4 changed in favor of IgG4.⁵⁷ Using 3 larger peptides to represent the entire Api m 1 antigen, 16 patients with bee venom allergy underwent peptide rush immunotherapy.⁵⁸ Bee venom peptide immunotherapy was well tolerated in all patients except for erythema more than 2 hours after administration in 2 patients. Peptide therapy increased total IL-10 and IFN- γ secretion, as well as allergen-specific IgG4 levels.⁵⁸ Others have used PLA₂ peptides based

on their binding affinity for commonly expressed HLA-DRB1 molecules on antigen-presenting cells.⁵⁹ In those peptide-treated patients late-phase IL-13 and IFN- γ production was reduced, and IL-10 production was increased in PLA₂-stimulated PBMCs compared with that seen in placebo-treated patients. Peptide treatment reduced late-phase cutaneous reactions and transient increases in bee venom IgG4 levels.⁵⁹

OTHER ROUTES OF ADMINISTRATION

Other modes of delivery have been investigated, such as oral, nasal, bronchial, epicutaneous, intraepithelial, intralymphatic, and sublingual.⁶⁰⁻⁶² Intranasal and intrabronchial immunotherapy are not currently used because of local symptoms associated with administration. In 165 patients with allergic rhinitis, 4 doses of grass immunotherapy administered directly into the inguinal lymph node was clinically as effective as 3 years of standard SCIT in symptom relief.⁶² Another grass-based immunotherapy study with epicutaneous patch administration found decreased rhinitis symptoms with therapy compared with that seen after placebo; however, eczema was frequently noted at the patch site for patients receiving active therapy.⁶²

Oral immunotherapy has been used in small trials for food desensitization to common foods, such as egg, milk, and peanut. In a small study 7 children with allergy to eggs underwent modified oral rush immunotherapy and subsequent home daily egg protein intake for 2 years.⁶³ At the end of the study, egg-specific IgG levels increased, whereas egg-specific IgE levels were unchanged. After 2 years of oral immunotherapy, all patients were able to tolerate more egg protein, with 2 patients exhibiting oral tolerance to eggs. In a small double-blind, placebo-controlled study, 20 children with milk allergy underwent a 3- to 4-month oral immunotherapy protocol.⁶⁴ Before treatment, the median milk threshold was 40 mg in both groups, with no change at the end of treatment in the placebo group, whereas the active oral immunotherapy group improved to 5100 mg by means of food challenge. Children who tolerated more than 2540 mg (2.5 oz milk) after oral immunotherapy continued daily milk powder intake. After 13 to 75 weeks of dosing, 6 of the 13 patients tolerated 16,000 mg without symptoms. Local reactions were common in about 17% of home doses given.⁶⁵ Another milk oral immunotherapy study used milk instead of milk powder as the substance for oral immunotherapy.⁶⁶ Thirty children were treated with increasing doses of milk at home after rush buildup and were compared with 30 children who strictly avoided milk and milk products. Of those children treated with milk oral immunotherapy for a year, 36% were able to tolerate 150 mL of milk daily, but 10% of the children stopped immunotherapy because of allergic symptoms. None of the 30 children with strict milk avoidance were able to tolerate 5 mL of milk.

Peanut allergy is the most common cause of death due to food allergies, with accidental ingestion a major concern. In a recent study oral desensitization with peanut protein frequently caused allergic symptoms, especially during the initial escalation day (93%) and buildup phase (46%), whereas only 3.5% of home doses resulted in allergic symptoms.⁶⁷ In 10,184 home doses of peanut oral immunotherapy, epinephrine was only required twice (0.02%). After a median time of 4.7 months, home maintenance dosing resulted in 93% of 29 patients tolerating 3.9 g of peanut protein (equivalent to more than 16 peanuts) in an open food challenge.⁶⁷ Markers of allergic inflammation, such as titrated skin

TABLE I. Types of immunotherapy currently used or under investigation for allergic diseases

Treatment	Allergens	Diseases
SCIT	Pollen, mold, dust mite, animals, venom	Allergic rhinitis, asthma, hymenoptera allergy
Addition of omalizumab	Ragweed, birch, cat, dog, dust mite	Allergic rhinitis, asthma
Allergoid modification	Grass, tree, dust mite	Allergic rhinitis, asthma
Allergoid + TLR-4 agonist	Grass, tree, ragweed	Allergic rhinitis
Immunostimulatory DNA sequences (CpG)	Ragweed	Allergic rhinitis, asthma
CpG + VLP	Dust mite, pollen	Allergic rhinitis, asthma
Wild-type recombinant	Grass, tree	Allergic rhinitis
Hypoallergenic recombinant	Tree, grass, dust mite, venom	Allergic rhinitis, hymenoptera allergy
Peptide	Animal, venom, grass, dust mite, weed	Allergic rhinitis, hymenoptera allergy
Oral immunotherapy	Food	Food allergy
SLIT	Pollen, mold, dust mite, animals, venom	Allergic rhinitis, asthma, hymenoptera allergy

prick test results, basophil activation, and peanut-specific IgE levels, decreased with oral desensitization, whereas peanut-specific IgG4 levels increased.⁶⁸

In 23 children with peanut allergy attempting long-term peanut oral immunotherapy, 14 patients were able to tolerate 500 mg of peanut.⁶⁹ A combination of oral immunotherapy and sublingual immunotherapy (SLIT) has shown efficacy in treating milk, egg, fish, wheat, and apple allergy.⁷⁰

Although there are promising results in several oral immunotherapy trials for food allergy, more data are needed to define the correct dosing regimen and ultimately clinical utility in routine clinical practice.⁷¹

Of the alternative routes for SCIT, SLIT has been studied the most and is an approved treatment in many countries. SLIT typically involves placement of the extract in a liquid formulation or pill under the tongue for 1 to 2 minutes followed by swallowing.⁷² An early meta-analysis of SLIT studies for allergic rhinitis included 22 trials and nearly 1000 patients.⁷³ The authors concluded that SLIT reduced symptoms by 42% and rescue medication use by 43%. A subsequent meta-analysis of asthmatic patients treated with SLIT concluded that SLIT was only mildly beneficial.⁷⁴ Between 1986 and June 2009, there have been 60 double-blind, placebo-controlled, randomized clinical trials (41 with grass or dust mite), and 48 had positive results in favor of SLIT, whereas 12 were totally or almost totally negative. The current meta-analyses favor SLIT in patients with pediatric asthma and allergic rhinitis and adults with allergic rhinitis.⁷⁵ Despite these results, some authors have found significant discrepancies and inconsistencies on meta-analysis evaluation of SLIT and conclude that there is not enough evidence to support the routine use of SLIT in patients with allergic asthma or allergic rhinitis.⁷⁵ Studies vary on many aspects, such as extract stability, daily dosing amounts, and frequency of dosing for different allergens. In addition, there is not a good placebo for SLIT, leading some to question the validity of the results.⁷⁶ Nonetheless, as discussed in this issue of the *Journal*, SLIT is effective in many patients, and recent US trials with grass and ragweed have demonstrated efficacy in patients with seasonal allergic rhinitis.

CONCLUSION

Allergy immunotherapy did not change dramatically in the first 75 years of its existence, but the last 25 years, especially the last decade, has produced an extensive literature on alternative approaches to traditional SCIT (Table I).⁷⁷⁻⁸² Multiple different approaches to increase regulatory T cell and cytokine levels and

reduce T_H2 cytokine production are at the forefront of these changes. The addition of omalizumab appears to improve the safety and efficacy of SCIT, whereas the use of TLR agonists increases the T_H1 response when added to SCIT. The modification of the allergen chemically or molecularly might make a more focused immunogenic and less allergenic vaccine. Finally, the use of differing routes of administration might facilitate the use of immunotherapy for a wider array of allergic diseases. As we find out more about the pathogenesis of allergic diseases and explore the immunologic changes induced by standard SCIT and alternative treatments, we will likely find even more ways to take advantage of that knowledge to modify allergic diseases.

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