

Review Article

SIT beyond respiratory diseases

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INTRODUCTION

The evidence is robust for the efficacy and preventive aspects of specific immunotherapy (SIT) for allergic rhinoconjunctivitis and allergic asthma.¹⁻³ However, in other allergic disorders that are not part of the respiratory disease spectrum, the evidence is beginning to emerge that these diseases also will respond to SIT.

Specific immunotherapy has been used to treat nonrespiratory diseases in several instances: sensitivity to Hymenoptera and fire ant stings has been shown to respond most favorably to SIT.⁴ Some evidence indicates that mosquito and other insect bite reactions are ameliorated with SIT.⁵ In addition, some studies of sublingual immunotherapy (SLIT) show benefits for reducing local reactions to Hymenoptera.⁶

No organ system in the human body is exempt from allergic reactions, and SIT works on many of these systems when employed to treat an allergic respiratory illness. Allergic diseases apart from the respiratory system also might respond to SIT directly. The largest two organ systems in the body, derived from the ectoderm and endoderm, probably represent the new frontiers for SIT. These are the skin and the mucosa of the gastrointestinal tract.

This review concentrates on these two areas, examining the state of art of SIT as it can be applied to treating allergic skin disorders and allergic immunoglobulin E (IgE)-mediated food allergy. The primary source of the reviewed studies was Medline, with the following medical subjects headings: food allergy, atopic dermatitis, immunotherapy (subcutaneous, oral, and sublingual), cow's milk, egg, peanuts, other foods. The computer search was supplemented with manual searches of references lists for all available review articles, primary studies, and abstracts from conferences. The search was limited, with rare exception, to English-language literature published through December 2010, including double-blind, randomized controlled trials comparing immunotherapy with placebo. However, uncontrolled studies and case reports also were included.

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The Food Allergens and Allergy Disorders

Allergic reactions to milk, egg, peanut, tree nuts, fish, shellfish, wheat, and soy account for most significant food allergies in the United States and in Europe, although any food can trigger an allergic response.^{7,8}

The adverse immune reactions to food proteins can range from immediate, potentially life-threatening reactions to chronic disorders. Most children outgrow their allergies to milk, egg, wheat, and soy; however, allergies to peanut, tree nuts, fish, and shellfish often persist into adulthood. The persistence of food allergy is variable, depending on the specific food allergen. Recent reports indicate that children are needing longer to outgrow their milk and egg allergies, with most developing tolerance in their teenage years rather than in early school-age, as previously thought.^{9,10} In contrast, only 20% of children with peanut allergy and 9% with tree nut allergy will develop tolerance.^{11,12}

Immune reactions to foods can be IgE-mediated, cell-mediated, or the result of a combination of IgE and non-IgE mechanisms. The IgE-mediated reactions usually occur within 2 hours of exposure; binding of food allergens by specific IgE on effector cells, such as basophils and mast cells, leads to mediator release (ie, histamine, tryptase, cysteinyl leukotrienes, prostaglandin D₂), causing a variety of symptoms that typically affect the cutaneous, respiratory, gastrointestinal, or cardiovascular systems.¹³

Cell-mediated reactions to foods include food proteins-induced enterocolitis syndrome (FPIES) and proctocolitis. FPIES is characterized by repetitive vomiting and diarrhea at least 2 hours after ingestion of the food trigger, with common triggers including milk, soy, and grains.¹⁴ Food-protein-induced proctocolitis is triggered by cow's milk or soy, and symptoms can be triggered by exposure through maternal breast milk. Infants are generally brought to medical attention for evaluation of blood-streaked stools. These infants are otherwise well in terms of growth and do not generally suffer adverse effects from blood loss such as anemia.¹⁵

Atopic dermatitis (AD) and eosinophilic gastroenteropathies are triggered by a combination of IgE and cell-mediated processes. Approximately 35% of children with moderate to severe atopic dermatitis have food allergies as a trigger.¹⁶ Conversely, convincing evidence exists that in some patients, aeroallergens, especially house dust mite (HDM), play a relevant role in eliciting or aggravating the eczematous skin lesions and may contribute to the flare-ups of eczema in those patients.^{17,18}

Because no treatments are available to cure or provide long-term remission from food allergy, allergen-specific treatments and strategies attempt to alter the allergic response to specific food allergens. Of note, new specific immunotherapeutic approaches currently under study are useful for the treatment of IgE-mediated food allergy. The trials covered patients with a large range of IgE-mediated disorders (from anaphylaxis¹⁹ to asthma, atopic dermatitis, urticaria²⁰). Currently no studies are available for non-IgE-mediated food allergies.

Clinical Effects of Specific Immunotherapy in IgE-Mediated Food Allergy

The current standard of care for food allergy focuses on 2 elements: strict avoidance of the allergen and emergency therapy in cases of accidental exposure.

A need clearly exists for “active” therapies that will allow food-allergic individuals to tolerate their specific food allergens. Moreover, the paradigm that delaying introduction of foods such as egg or peanuts may protect against allergy is currently under revision.^{21,22} Recently, multiple studies have been published, and others are underway at various stages of research, focused on the practice of oral food immunotherapy.

Both SLIT and oral immunotherapy (OIT) have been studied for treatment of IgE-mediated food allergy, although reports on OIT thus far have been more extensive.

In SLIT, allergen exposure occurs via a liquid extract placed under the tongue, and studies have documented success with hazelnut, cow’s milk, and kiwi allergies.^{23–27} During OIT, food is mixed in a vehicle (safe food) and ingested in gradually increasing dose. Conversely, in some trials, fresh material (cow’s milk), without vehicle, also was consumed by patients. Results of OIT studies generally have been encouraging. In one of the earlier OIT studies, Patriarca et al.²⁸ desensitized 75% of their patients to a variety of food allergens.

Meglio et al.²⁹ successfully desensitized a similar percentage of milk-allergic patients.

Whereas most published OIT protocols involve a period of months to reach maintenance doses, a rush protocol was evaluated in 9 children with severe and persistent cow’s milk allergy.³⁰ Patients were admitted to the hospital, and rush OIT was performed in a single-blind fashion, using soy milk for blinding.

Six of nine were able to advance to maximal doses within 3 to 7 days; reactions were common but generally mild; only 1 patient was treated with salbutamol for wheezing.

The OIT with peanuts has been documented recently, with studies carried out in the United States.^{31,32} A large open-label peanut OIT study by Jones et al.³³ showed that oral immunotherapy induces clinical desensitization to peanut, with significant longer-term humoral and cellular change.

Blumchen et al.³⁴ carried out a study comparing rush oral immunotherapy with long-term buildup protocol in 23 children who had peanut anaphylaxis. Only 5 participants were

able to tolerate at least 500 mg whole peanut after 7 days—OIT rush protocol. In contrast, 14 participants reached the same maintenance dose using a long-term (up to 20 months) protocol.

Four patients dropped out because of allergic reactions and were considered treatment failures. Rush oral immunotherapy was not successful in most children with peanut allergy. In contrast, a long-lasting buildup protocol for peanut OIT appears to be safe and effective in reaching clinically relevant protective doses for high-risk patients with peanut allergy.

Buchanan et al.²⁰ treated 7 children with mild symptoms (urticarial rash) allergic to egg; 6 of them tolerated significantly more egg protein than at study onset.

OIT: Studies with Control Groups

Studies that include control groups are important to understand the impact of OIT. Staden et al.³⁵ compared tolerance induction and elimination diet in 47 children allergic to cow’s milk (CM) or hen’s egg. The patients were randomly assigned to OIT or elimination diet as a control group. Reevaluation of clinical relevant food allergy was performed by food challenge after a median of 21 months: Interestingly children in OIT received a secondary elimination diet for 2 months before a double-blind placebo-controlled food challenge (DBPCFC) to evaluate persistence of induced oral tolerance. In this study, a similar percentage (35%) in both the treatment and controlled group displayed tolerance by passing the DBPCFC off therapy; although a number of “partial responders” to OIT were seen, which increase the rate (total plus partial) of response(s) to 64%. Therefore, the patients who reached total tolerance were able to break off the intake of “previous culprit foods” without the risk of further appearance of allergic symptoms.

Longo et al.¹⁹ studied 60 children 5 years of age or older with histories of severe allergic reactions to milk ingestion.

Approximately 80% of participants in this study had milk-specific IgE levels greater than 100 kU/L, with mean skin prick test wheal sizes of 11 to 12 mm. Half received immunotherapy for 1 year, and half were observed with conventional elimination management. The OIT was carried out for 10 days in the hospital and continued until the dose of 20 mL of pure CM ingested by the children. Afterward, the patients were discharged, and the trial was carried out daily at home until the dose of 150 mL was reached. Of those treated with OIT, 36% were able to tolerate a single feeding of 150 mL; 54% could ingest 5 to 50 mL, and 10% (3 children) interrupted the study because of the appearance of serious unwanted effects.

Conversely, most of children in the observation group saw no change in their milk reaction threshold, and none were able to tolerate 5 mL.

Almost all children in the OIT group experienced allergic symptoms during the protocol, primarily involving urticaria and angioedema.

Skiprak et al³⁶ studied by means of a randomized, double-blind, placebo-controlled trial 20 children allergic to CM. The patients were randomized to milk or placebo OIT (2:1 ratio).

Participants had to tolerate a minimum dose of 12 mg (cumulative dose, 23.7 mg) to proceed with home dosing. Once a dosing of 500 (equivalent to 15 mL of milk) was achieved, children continued on that dose daily for 13 weeks, after which they underwent their next DBPCFC.

Twelve in the active group and 7 in the placebo group completed the study. After OIT, the median cumulative dose inducing a reaction in the active treatment group was 5,140 mg (range, 2,540–8,140), whereas all patients in the placebo group reacted at 40 mg.

Pajno et al³⁷ evaluated the safety and efficacy of OIT by means of a new study's protocol. This was carried out by performing a weekly outpatient dose increasing protocol comprising 28 visits during approximately 4 months. Thirty children with confirmed cow's milk allergy via DBPCFC were randomized to receive active therapy of sham protocol with the use of soy.

The primary outcome was the reduction in clinical sensitivity as demonstrated by change in threshold dose via DBPCFC, and the secondary outcome was the immunologic change associated with this procedure. The OIT was effective, with the tolerated "full" milk dose of 200 mL in 10 of 13 individuals, partial tolerance in 1, and 2 who required discontinuation because of severe reactions associated with the OIT protocol (Table 1).

Regarding immunologic results, no change was seen in specific IgE levels; however, in the actively treated group, an increase was seen in IgG4 levels to cow's milk.

Clinical Effects of Immunotherapy in Atopic Dermatitis

Atopic dermatitis is an eczematous disorder of the skin that affects up to 20% of children and 1% to 3% of adults.³⁸ In terms of diagnostic tools, that total IgE and allergen-specific

IgE are elevated in the sera of most of the AD patients became clear. However, a subgroup of children and adults patients with AD exists in which IgE-mediated mechanisms seem to play a marginal role.³⁹ Up to 35% of children younger than 5 years of age with moderate to severe AD have food allergies as a trigger.¹⁶ Removal of culprit foods results in significant improvement in skin symptoms for these children. Conversely, children who developed AD after 12 months were less likely to have concurrent food allergies.⁴⁰

Inhalants also have been implicated as a factor of AD. The role of aeroallergens leading to both symptoms and signs of AD is now well recognized.⁴¹ Exposure to dust mites either through the respiratory tract or directly on the skin can lead to exacerbations of AD. Moreover, facilitated by their high enzymatic activity, HDM allergens are capable of penetrating the impaired epidermal skin barrier in patients with AD to get access to immune cells such as mast cells and dendritic cells.

This is of particular importance in view of the finding that mutation in the fillagrin gene might be associated with AD and the impaired skin barrier in these patients and predispose a subgroup of patients with AD to the development of several sensitizations via this deficient skin barrier shield.^{42,43}

Specific immunotherapy against inhalant allergens sensitization is not generally indicated for AD without concomitant rhinoconjunctivitis or mild allergic asthma present, because of the risk of exacerbations of eczema.⁴⁴

So far, only few controlled studies with SIT were carried out on patients suffering from extrinsic form IgE-mediated AD.

A systemic analysis of all controlled and uncontrolled studies on SIT in AD published until the end of 2006 identified 23 studies (11 controlled studies, 10 uncontrolled studies, and 2 case reports) and showed high heterogeneity; most of them were carried out with HDM aeroallergens.⁴⁵

Most studies, regardless of whether controlled or uncontrolled or single reports, showed a trend for amelioration of

Table 1. Oral Food Desensitization for IgE-Mediated Food Allergy: Randomized Controlled Study

Study	Patients (N)	Success rate	Comments
Longo (35) 2008 Cow's milk (CM) and egg	CM 14 Egg 11 Control group 20 Age (0.6–12.9 y)	- 9/35 (36%) Permanent tolerance - 3/25 (12%) Tolerance with regular intake (desensitization) - 4/25 (16%) Achieved partial tolerance	The first randomized clinical trial of OIT. The rate of spontaneous food allergy resolution in the control group (7/20; 35%) was similar to the treatment group
Staden (19) 2007 Cow's milk (CM)	CM 60 30 Active group 30 Control group Age (5–17 y)	- 11/30 (37%) Tolerated 150 mL of CM - 13/30 (53%) Tolerated 5–150 mL	The first study including children with previous anaphylaxis to CM
Skiprak (36) 2008 Cow's milk (CM)	CM 20 active to placebo ratio 2:1 Age (6–21 y)	- 12 (92%) of active group reached the dose 5,140 mg of CM (range, 2,540–8,140 mg) - No change in the placebo group	The first double-blind, placebo-controlled clinical trial for OIT
Pajno (37) 2010 Cow's milk (CM)	CM 30 active to placebo ratio 1:1 Age (4–13 y)	- 10 (76%) of active group tolerated 200 mL CM - No change in the placebo group	The first blinded trial with the weekly updosing regimen carried out in 18 weeks

AD under SIT. However, improvement in the placebo group compared with active was superior in 1 study,⁴⁶ and no difference in the effect of SIT compared with conventional therapy was reported in another study.⁴⁷

The main weakness of the studies in the past is that most of these studies were performed without a placebo group. Moreover, among the trials are basic differences, such as schedules used for the trials, inclusion criteria for the patients selected for the studies, the duration of SIT, and the nature of allergen extracts.

Therefore, none of the studies included in the review had sufficient power to achieve some conclusions on this field. Conversely, 3 studies could be highlighted as of outstanding interest.

Werfel et al⁴⁸ performed a controlled randomized multicenter study in 89 adults with chronic course of AD allergic to HDM, of whom 51 completed the study. Subcutaneous immunotherapy (SCIT) with HDM (*Dermatophagoides pteronyssinus*/D. Farinae), applying maintenance doses of 20, 2000, and 20,000 standard quality units in weekly intervals for 1 year, was carried out. The severity scoring of AD (SCORAD) values declined in a dose-dependent manner and was significantly lower in the two high-dose groups (2,000 and 20,000 SQU) compared with the low group of 20 SQU, after 1 year of treatment; the use of topical corticosteroids was significantly reduced with higher dose. Bussmann et al⁴⁹ performed an open-label study with HDM allergy via the subcutaneous route in 25 AD patients with IgE-mediated sensitizations against HDM.

Subjective and objective SCORAD improved significantly within 4 weeks of treatment; this improvement advanced further during the maintenance phase, with a reduction of up to 60% compared with SCORAD at baseline.

Pajno et al⁵⁰ studied 56 children age 5 to 16 years with AD sensitized against HDM; the patients were treated with either SLIT or placebo for 18 months. Significant improvement measured by SCORAD in the active group was observable after 9 months of treatment; similarly, a significant reduction was seen in the use of medications only in children treated with HDM vaccines. Significant difference in the considered parameters was found only in patients with a mild to moderate AD, whereas patients with severe conditions had only

marginal benefits (Table 2). Note that SLIT had to be discontinued in 2 patients because of a severe exacerbation of dermatitis.

Altogether, with regard to side effects, severe exacerbation of AD is reported in up to 20% of the cases during immunotherapy.^{44,51} A study carried out in parallel with SCIT or SLIT reported adverse reactions in 14% in the sublingual as opposed to 19% in subcutaneous group.⁵² Therefore, the appearance of serious cutaneous unwanted effects could be possible during treatment with allergen immunotherapy in patients suffering from an allergic extrinsic form of AD, particularly in those with a severe form.

Food Immunotherapy: Future Directions

A recent review on the future of SIT looked at some of the newer methodologies being developed. These include oral immunotherapy, SLIT, epicutaneous immunotherapy, peptide immunotherapy, use of adjuvants, recombinant allergens, and hybrid molecules.⁵³ Omalizumab combined with SIT has been shown to be more effective than either alone.⁵⁴ The use of pharmacologic agents combined with SIT may also prove useful. Chinese herbal medications may lead to an alternate approach. Scurlock and Jones⁵⁵ in 2010 reviewed the uses of immunotherapy for food allergy, concluding, “Advances in our understanding of the immunologic mechanisms underlying food allergy and of the elegant complexities of the mucosal immune response have resulted in substantial progress toward definitive therapeutic options for food-allergic individuals”.

CONCLUSIONS

Food allergies and atopic dermatitis therapy represent a frontier in which the application of SIT may prove more fruitful when added to current therapeutic options.^{13,53} The preliminary data are encouraging; however, new studies must answer multiple questions, including optimal dose, degree of protection, efficacy for different ages, adequate patients' selection, severity and type of both food allergy and AD responsive to treatment, and safety of immunotherapy. However, using current knowledge on both gastrointestinal and cutaneous immunity, researchers are investigating immunomodulatory

Table 2. Extrinsic Form IgE-Mediated Atopic Dermatitis (AD): Randomized Controlled Study

Study	Patients (N)	Success Rate	Comments
Werfel (48) 2006 SCIT HDM	89 Adult patients 38 (42%) drop out 1 year treatment	37 (72%) Treated with high dose of SCIT	The first randomized SCIT trial in patients with AD High rate of drop out
Pajno (50) 2007 SLIT HDM	56 Children Active to placebo Ratio 1:1 Age (5–16 y) 8 (16%) Drop out 18 Months of treatment	Improvement of symptoms only in children with mild to moderate AD	The first double-blind placebo-controlled study with SLIT. Serious side effects with exacerbation of eczema in 2 patients

approaches that provide “active” therapy for both food allergy and AD.

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