

Food allergen immunotherapy: Current status and prospects for the future



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Activity Objectives:

1. To review the current status of food immunotherapy, including oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT).
2. To discuss the proposed underlying mechanisms involved in food immunotherapy.
3. To discuss modified allergen immunotherapy and the potential role for adjunctive therapies currently under consideration.

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Food allergy is a common condition for which the only currently approved treatments are avoidance of the allergenic food and administration of emergency medications on accidental exposure. Over the past 10 years, significant advances have been made in the field of food immunotherapy, including oral immunotherapy, sublingual immunotherapy, and, more recently, epicutaneous immunotherapy. Each of these approaches are intended to induce some level of desensitization with chronic or repeated exposure to the allergenic food protein, although the risks and potential benefits of each treatment differ significantly. Although new data are emerging at a rapid pace and progress has been substantial, a number of important issues

need to be addressed before introduction of these therapies into clinical practice. Furthermore, it is entirely possible that advances in this field will render these current approaches obsolete over the next 20 to 30 years as new and better therapies are developed. (*J Allergy Clin Immunol* 2016;137:973-82.)

Key words: Food allergy, peanut allergy, egg allergy, milk allergy, immunotherapy, oral immunotherapy, sublingual immunotherapy, epicutaneous immunotherapy, omalizumab

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Food allergy (FA) is very common, affecting up to 8% of young children and 3% to 6% of the entire US population,¹⁻⁴ and its prevalence appears to have increased significantly over the past 15 to 20 years.^{4,5} The only currently approved treatments for FA are avoidance and administration of emergency medications on accidental exposure. Although many young children with FA will develop natural tolerance over time, for many, it persists into adolescence and adulthood, including most with peanut and tree nut allergy and important subsets of patients with milk and egg allergy.^{1,3,6,7} FA causes significant impairment in quality of life⁸ and can lead to nutritional deficiencies⁹ and, even with

Abbreviations used

DBPC: Double-blind, placebo-controlled
 EPIT: Epicutaneous immunotherapy
 FA: Food allergy
 FDA: US Food and Drug Administration
 OFC: Oral food challenge
 OIT: Oral immunotherapy
 RCT: Randomized controlled trial
 SCIT: Subcutaneous immunotherapy
 SLIT: Sublingual immunotherapy
 SU: Sustained unresponsiveness

meticulous avoidance, frequent and potentially life-threatening reactions.^{10,11} Given the prevalence of FA and its associated morbidities, safe and effective therapies are highly desirable.

Immunotherapy relies on the delivery of increasing doses of specific allergens over time with the goal of developing desensitization and eventual tolerance. Although the exact mechanisms underlying allergen immunotherapy are still not fully understood, it is known to induce allergen-specific regulatory T cells, which suppress T_H2 responses. This response is coupled with increases in levels of allergen-specific IgG₄ antibodies and reductions in mast cell and basophil activation and mediator release.¹²⁻¹⁵

Over the past century, immunotherapy has been successfully used to treat asthma, allergic rhinitis, and venom hypersensitivity. Published case reports of immunotherapy for FA date back to at least the 1940s,¹⁶⁻²⁰ but the first randomized placebo-controlled study was not published until 2005.²¹ In the 1990s, an attempt to use subcutaneous immunotherapy (SCIT) for peanut allergy resulted in an unacceptably high rate of systemic reactions, such that this approach was largely abandoned.²² Therefore subsequent studies have focused on alternative routes of delivery or potential modification of allergenic proteins in an effort to induce tolerance while at the same time reducing risk. Here we will review the current status of oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT), as well as other novel approaches for the potential treatment of the patient with persistent FA.

OIT

OIT is accomplished by mixing the allergenic food into a vehicle and ingesting it in gradually increasing doses. Protocols have varied considerably with regard to dosing and the type of food used, with some using commercially available foods (eg, liquid milk) and others using specifically prepared products (eg, defatted peanut flour). Although these therapies can essentially be purchased in the grocery store, most OIT research has been and should be conducted with US Food and Drug Administration (FDA) oversight, which requires Investigational New Drug status with FDA-regulated standards and safeguards. For example, allergenic proteins must be identified and quantified, and the product must be shown to be free of microbial contaminants.

Although the details vary considerably, most OIT protocols include an initial dose escalation, followed by a gradual dose build-up and a prolonged maintenance phase (Fig 1).^{13,23,24} Initial dose escalation is typically conducted on a single day, beginning with an extremely small dose that is rapidly increased (eg, starting with 0.1 mg of the food protein and increasing in doubling doses

to a maximum of 10 to 25 mg).²⁵⁻²⁷ The intent of the initial escalation is to begin and remain at subthreshold levels and identify a safe starting dose for home administration. In the build-up phase dose escalations, which vary in increments from 25% to 100% in different protocols, are typically conducted under a physician's supervision every 1 to 2 weeks, with daily home doses in between until the target maintenance dose is achieved. Studies also differ markedly in both the maintenance dose and duration of treatment, with doses ranging from 300 to 4000 mg and durations ranging from months to years. Tables I to III²⁵⁻⁴¹ show some of the variability in study design in terms of maintenance dosing, duration of therapy, and outcomes.

Efficacy of OIT

Although individual responses vary considerably, OIT will induce significant desensitization in most patients who are able to tolerate the therapy.^{25-30,42,43} Desensitization is defined as a temporary increase in the threshold for reactivity in which maintenance of the desensitized state requires continued exposure to prevent the recurrence of reactivity. In some trials subjects who are successfully desensitized will then discontinue treatment, typically for 4 to 8 weeks, after which another oral food challenge (OFC) is performed to determine whether they have sustained unresponsiveness (SU), which is defined as no increase in reactivity after this period of avoidance. Although initial studies used the term tolerance rather than SU, that term has largely been abandoned because it clearly overestimates the potential of these therapies, with even SU not seen in a majority of treated subjects.^{26,28,30,31,43-46} This lack of sustained protection has important implications for the future of food immunotherapy and reinforces the experimental nature of this treatment. Furthermore, there are a paucity of long-term follow-up studies, and those that have been done indicate that even patients who appear to be completely desensitized can lose protection over time.⁴⁴

Immunologic changes with OIT

The key mechanisms by which OIT induces desensitization and potentially longer-term protection are still under investigation. Early immunologic changes include an increase in food-specific IgG₄ levels and decreased basophil and mast cell responsiveness, with decreased skin test responses and basophil activation seen in the first few months of treatment.^{26,28,29,45} Allergen-specific IgE levels increase initially and then gradually decrease, and some studies have shown that OIT alters the binding pattern of antigen to IgE, possibly through changes in the diversity of epitope recognition or altered antigen affinity.⁴⁷ After 6 to 12 months, there appears to be a shift away from T_H2 cytokine production toward a T_H1 profile.²⁹ Immune suppression by regulatory T cells and clonal anergy occur later in the course of OIT, including increased function of antigen-specific CD4⁺CD25⁺ forkhead box protein P3-positive regulatory T cells.^{42,45} Finally, consistent with the potentially transient clinical efficacy of OIT, it has also been shown that many of these immunologic changes are transient, even while receiving maintenance therapy.⁴⁵

Representative OIT trials

Peanut OIT. For further information on peanut OIT, see Table I.

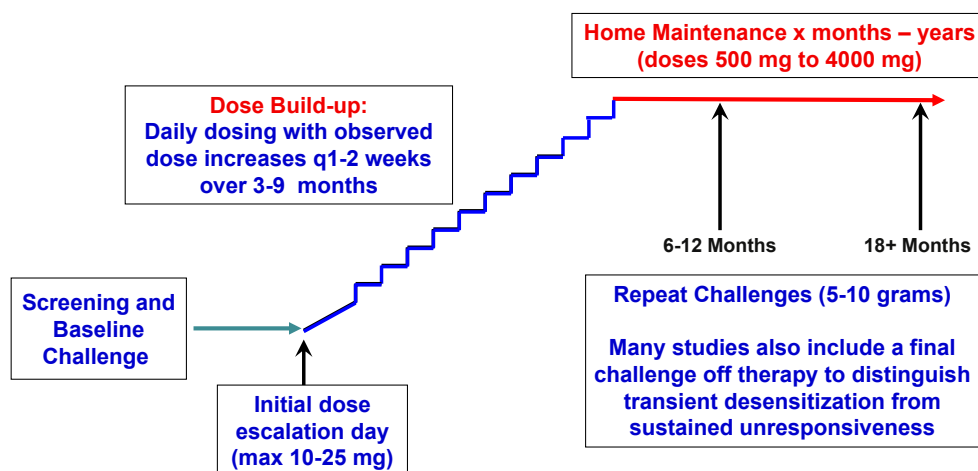


FIG 1. Schematic representation of the typical approach to OIT. For SLIT, the overall scheme is similar, with far lower goal doses and a somewhat more rapid dose build-up.

TABLE I. Peanut OIT studies

Reference	Year	Design	Samples size	Subject age (y)	Maintenance dose (mg)	Duration	Primary outcome
Jones et al ²⁹	2009	Open label	29	1-16	1800	36 mo	93% Passed 3.9-g peanut OFC
Blumchen et al ³⁰	2010	Randomized open label	23	3-14	500	7-d Rush escalation, 8-wk maintenance period	64% Reached maintenance of 500 mg of peanut
Varshney et al ²⁷	2011	Randomized, placebo controlled	19	3-11	2000	48 wk	84% Passed 5000-mg peanut OFC
Anagnostou et al ³²	2011	Open label	22	4-18	800	32 wk	64% Tolerated 6.6-g OFC
Anagnostou et al ³³	2014	Randomized, controlled	39	7-16	800	26 wk	62% Tolerated 1400-mg challenge
Vickery et al ²⁸	2014	Open label	24	1-16	Up to 4000	Up to 5 y	50% SU to 5000-mg OFC after 4-wk avoidance
Narisety et al ³¹	2014	Randomized, placebo controlled	16	7-13	2000	12 mo	OIT > SLIT in OFC threshold, low rate of SU

TABLE II. Egg OIT studies

Reference	Year	Design	Sample size	Subject age (y)	Maintenance dose (g)	Duration (mo)	Primary outcome
Buchanan et al ³⁴	2007	Open label	7	1-16	0.3	24	57% Passed 8-g OFC
Vickery et al ³⁵	2010	Open label	8	3-13	0.3-3.6	18-50	75% Passed OFC 1 mo after stopping OIT
Burks et al ²⁶	2012	Randomized, placebo controlled	40	5-11	1.6	22	75% Passed 10-g OFC but SU in only 28% at 6-8 wk later

After early case reports of successful peanut OIT,^{48,49} the first open-label trial was published in 2009.^{23,29} This study showed successful induction of desensitization, an overall reassuring safety profile, and humoral and cellular changes demonstrating immune modulation with a maintenance dose of 1800 mg of peanut protein. At 36 months, 27 (93%) of 29 patients who completed the protocol were able to tolerate an OFC of 3.9 g.²⁹ The first randomized, double-blind, placebo-controlled (DBPC) trial of peanut OIT in 2011 reported that 16 subjects receiving active OIT tolerated a median dose of 5 g (approximately 20 peanuts) compared with the placebo group of 9 subjects who tolerated a median of 280 mg, with 3 subjects receiving active therapy withdrawing because of adverse reactions.²⁷

In 2011, a prospective cohort study of peanut OIT reported on 22 children receiving maintenance dosing of 800 mg for 32 weeks,³² demonstrating a significant reduction in peanut reactivity, with 86% of subjects tolerating up dosing and 14 (64%) of 22 tolerating a 6.6-g OFC at completion of treatment. In 2014, the same group reported a randomized controlled trial (RCT) of peanut OIT, also using a maintenance dose of 800 mg, with desensitization demonstrated in 62% in the active group compared with 0% in the avoidance group.³³

The first study of SU after peanut OIT was reported in 2014, demonstrating that 50% of subjects remained nonreactive 4 weeks after stopping treatment.²⁸ Another study of peanut OIT and SU found that 7 (35%) of 20 subjects were not reactive after 3 months

TABLE III. Milk OIT studies

Reference	Year	Design	Samples size	Subject age (y)	Maintenance dose	Duration	Primary outcome
Meglio et al ³⁶	2004	Open label	21	6-10	200 mL	6 mo	72% Desensitization to 200 mL of cow's milk daily
Longo et al ³⁷	2008	Randomized, open label	30	5-17	150 mL	10-d Rush escalation, 1 y of maintenance	36% Tolerant (≥ 150 mL) and 54% partially tolerant (5-150 mL)
Skipak et al ³⁸	2008	Randomized, placebo controlled	13	6-17	500 mg	23 wk	Median OFC threshold increased from 40 to 5,140 mg after OIT
Narisety et al ³¹	2009	Open label (follow-up)	13	6-16	500-4,000 mg	3-17 mo	Median OFC threshold of 7,000 mg (with 33% tolerating 16,000 mg)
Pajno et al ⁴⁰	2010	Randomized, placebo controlled	15	4-10	200 mL	18 wk	67% Tolerant to 200 mL of cow's milk
Martorell et al ³⁹	2011	Randomized, placebo controlled	30	2-3	200 mL	1 y	90% Showing complete desensitization
Keet et al ²⁵	2012	Randomized, placebo controlled	20 for OIT	6-17	1,000-2,000 mg	60 wk	70% Desensitized to 8-g OFC, SU in 40% after 6 wk
Wood et al ⁴¹	2015	Omalizumab DBPC, open-label OIT	57	7-32	3,300 mg	24 mo	80% Desensitized to 10-g OFC, SU in 42% after 8 wk

of avoidance, with only 3 of those 7 remaining unresponsive 3 months later (ie, 6-month SU rate of 13%).⁴²

Egg OIT. For further information on egg OIT, see Table II.

Three early pilot studies of egg OIT demonstrated overall positive results.^{18,34,50} In a follow-up of one of these studies, higher individualized doses (median, 2400 mg) were used for a longer duration (median, 33 months), and 6 of the original 8 subjects were determined to have SU 4 weeks after stopping treatment.³⁵ Two RCTs of egg OIT were subsequently published, comparing treatment with avoidance,^{43,51} both demonstrating significant differences between the treated and control subjects, with complete or partial desensitization demonstrated in 60% to 70%.

In 2012, the results of the first multicenter DBPC trial of egg OIT were reported.²⁶ The maintenance phase of the study consisted of 2 g of egg protein daily, with OFCs performed at 10 and 22 months. At 10 months, none of the placebo-treated subjects ($n = 15$) were desensitized compared with 55% ($n = 40$) of those receiving active OIT. After 22 months, 30 (75%) of 40 subjects were effectively desensitized, but only 11 (28%) demonstrated SU on rechallenge 6 to 8 weeks later. Other studies of egg OIT have included small RCTs with desensitization rates of 80% to 90%, including children with severe egg allergy, and 2 studies using rush protocols with desensitization induced in as little 5 days.⁵²⁻⁵⁵

Milk OIT. For further information on milk OIT, see Table III.

As with egg, early studies of milk OIT demonstrated successful desensitization in a majority of subjects, although there was great variability in both dosing and end points,^{18,36,50} and several other open-label studies also demonstrated overall success.⁵⁶⁻⁵⁸ In 2008, Longo et al³⁷ reported an RCT of 60 children with a history of severe milk allergy randomized to milk OIT or avoidance. At 12 months, no participants in the control group passed their OFC compared with 11 (36%) treated subjects who were completely tolerant and 16 (54%) with partial tolerance. The first DBPC OIT trial, in which 21 subjects were treated for 3 to 4 months with 500 mg of milk protein or placebo, also occurred in 2008.³⁸ In those receiving active therapy, the median milk challenge threshold increased from 40 mg at baseline to

5,140 mg after treatment, with no change in the placebo group. A follow-up open-label study with individualized, ongoing milk intake demonstrated the ability to tolerate from 1,000 to 16,000 mg of milk protein (median of 7,000 mg, with 33% tolerating 16,000 mg at the final OFC).⁵⁹

Another RCT published in 2012 compared milk OIT with milk SLIT in 30 children.²⁵ The study showed that the OFC threshold, as well as the proportion desensitized, was greater with OIT compared with SLIT but that OIT was associated with more adverse effects. SU was also studied, demonstrating that only 40% of subjects receiving milk OIT were still nonreactive after 6 weeks of avoidance, with 2 subjects losing protection after just 1 week off therapy.

OIT to other foods and multiallergen OIT

Although most research to date has focused on milk, egg, and peanut, there is great interest in the potential to treat other common food allergies. Studies of OIT to wheat, tree nuts, fish, and possibly other foods are currently underway (see www.clinicaltrials.gov). Given the fact that so many children are allergic to more than 1 food, there is also great interest in the potential to treat multiple foods simultaneously. Numerous multiallergen OIT studies are also currently underway, some with and some without coadministration of omalizumab. The additional challenge in treating multiple foods relates to the need to provide adequate doses of each food without significantly increasing risk. Although only preliminary results have been published, data from 1 study demonstrated similar safety and efficacy when comparing peanut OIT with multifoed OIT,⁶⁰ and another demonstrated that pretreatment with omalizumab permitted successful rush OIT to multiple foods.⁶¹

Safety of OIT

Adverse reactions are very common with OIT, with similar rates reported for milk, egg, and peanut. Local symptoms, such as oral pruritus and transient abdominal pain, are most common, and reactions are generally mild, requiring either no treatment or

TABLE IV. SLIT studies

Reference	Year	Food	Design	Sample size	Subject age (y)	Maintenance dose (mg)	Duration	Primary outcome
Enrique et al ²¹	2005	Hazelnut	Randomized, placebo controlled	23	19-53	13.25	8-12 wk	Significant increase in OFC threshold with active SLIT
Kim et al ⁷¹	2011	Peanut	Randomized, placebo controlled	18	2-10	2.5	12 mo	OFC threshold 20 times greater SLIT vs placebo (median, 1710 vs 85 mg)
Fleischer et al ⁷²	2013	Peanut	Randomized, placebo controlled	37	12-36	1.4-3.7	44 wk	70% Receiving peanut SLIT were responders vs 15% receiving placebo
Keet et al ²⁵	2012	Milk	Randomized, SLIT vs OIT	10 for SLIT	6-17	7	60 wk	Median OFC threshold increased 40-fold (2458 mg) from baseline
Narisety et al ³¹	2015	Peanut	DBPC SLIT vs OIT	20	7-13	3.7	12 mo	Median OFC threshold increased from 21 to 496 mg
Burks et al ⁷³	2105	Peanut	Open label (follow-up)	37	12-36	1.4-3.7	36 mo	Four (10.8%) of 37 desensitized to 10 g of peanut powder, all 4 with SU

antihistamines alone. Many patients appear to benefit from pretreatment with H₁ antagonists, H₂ antagonists, or both, although these data have not been reported in any rigorous manner. Abdominal pain is the most common symptom leading to treatment withdrawal, and moderate reactions, such as wheezing, vomiting, and urticaria, occur in a small percentage of subjects receiving doses of any size. However, given that doses are given daily, the risk for each patient over an extended course of treatment is substantial. For example, in one study of milk OIT, 47% of subjects had moderate reactions over the course of treatment,³⁹ and in a study of peanut OIT conducted in practice settings, 95 reactions requiring epinephrine occurred during treatment for 352 patients.⁶² More severe reactions requiring treatment with epinephrine and β -agonists are most common during dose escalation but can also occur during maintenance therapy.^{31,37-40} It is especially concerning that most severe reactions occur unpredictably with a dose that has been previously tolerated and are often but not always associated with cofactors, such as infection, exercise, or allergen coexposure.^{23,33,38,59}

A particular obstacle to bringing these treatments to clinical practice is the large subset of patients who cannot tolerate OIT. Overall, 10% to 20% of subjects have withdrawn from OIT trials, with rates as high as 36%, because of adverse events. Although some withdraw because of anaphylaxis or other acute reactions, the vast majority withdraw because of chronic intolerable gastrointestinal symptoms. Eosinophilic esophagitis has been documented in some of these cases, and it is not presently clear how frequently undiagnosed eosinophilic esophagitis can complicate OIT.^{63,64}

Long-term efficacy

Relatively few studies have examined SU after OIT, much less longer-term efficacy and safety. Meglio et al⁶⁵ reported that 4 years after completing open-label milk OIT, 14 (70%) of 20 subjects who achieved partial or full desensitization were still able to tolerate milk, and no child had received emergency care for adverse reactions. Keet et al⁴⁴ described the long-term follow-up of 2 milk OIT studies 3 to 5 years after study completion. They found that only 31% of patients were tolerating uncooked milk without symptoms, 22% limited their milk consumption because of symptoms (including anaphylaxis), 6% ate only trace

amounts of milk, and 16% avoided milk entirely. These results were both surprising and concerning given that most of the children were tolerating large amounts of milk at study completion.

Meta-analyses

Several systematic reviews and meta-analyses have now been published regarding OIT. Two focused on milk, with similar conclusions.^{66,67} One concluded that although OIT appears to be efficacious, the quality of evidence is low because of small studies with inconsistent methodology, whereas the second wrote that the potentially large benefit of milk OIT must be counterbalanced by frequent and sometimes serious adverse effects. Both recommended larger well-controlled studies with consistent methodology before considering OIT for clinical use. In the largest review to date, which included 18 RCTs with various foods, the authors concluded that there is strong evidence that OIT induces immunomodulatory changes and promotes desensitization but that given the paucity of evidence on longer-term safety and effectiveness, OIT should not currently be used outside the research setting.⁶⁸

SLIT

With SLIT, the food protein is delivered sublingually in a liquid form and then usually held for 2 minutes and swallowed. SLIT is thought to capitalize on the tolerogenic antigen-presenting cells in the oral mucosa.⁶⁹ It is further thought that SLIT efficacy can be enhanced by exposure to the food protein in its intact form before possible epitopes are broken down through gastric digestion.⁷⁰ However, SLIT dosing and potential efficacy are limited by the concentration of available extracts and the volume of liquid that can be held sublingually. Typical doses start with microgram levels of the allergenic protein and increase to 1 to 10 mg by maintenance.

Representative SLIT studies

For further information on representative SLIT studies, see Table IV.^{21,25,31,71-73}

In 2005, Enrique et al²¹ reported the first DBPC trial for the treatment of FA, with 23 subjects randomized to active hazelnut SLIT or placebo. After 8 to 12 weeks of treatment, 11 actively treated subjects reached the target dose, 5 (42%) of whom were

able to ingest 20 g of hazelnut without symptoms compared with only 1 of 11 in the placebo group. The mean tolerated dose increased from 2.3 to 11.6 g in the active group.

Two DBPC trials of peanut SLIT have been published. The first enrolled 18 children randomized to SLIT or placebo with a goal dose of 2.5 mg.⁷¹ All 11 children receiving active therapy completed the desensitization protocol, and the median dose in the posttreatment OFC was 1710 mg versus 85 mg in the placebo group ($P = .011$). Dosing side effects were primarily oropharyngeal and uncommonly required treatment.

In the second study 40 adolescents and adults were treated with peanut SLIT or placebo, with a maximum dose of 1.4 mg.⁷² After 44 weeks of treatment, all subjects underwent a 5000-mg OFC, after which the placebo group crossed over to a dose of 3.7 mg. At the 44-week OFC, 14 of 20 subjects receiving active therapy were considered responders compared with 3 of 20 subjects in the placebo group ($P < .001$). The median tolerated dose in the responders increased from 3.5 to 496 mg. Of 10,855 doses through week 44, 63.1% were symptom free, and when excluding oral-pharyngeal symptoms, 95.2% were symptom free. More recently, a 3-year follow-up of this study came to the same overall conclusion that peanut SLIT induces “a modest level of desensitization” with an excellent safety profile. This long-term study also revealed that only a minority of subjects were willing to continue therapy for the full 3 years and that only 4 (10.8%) of 37 subjects achieved SU.⁷³

Studies comparing OIT and SLIT

Only 3 studies have directly compared OIT with SLIT, one of which was conducted retrospectively.⁷⁴ As noted above, in 2012, Keet et al²⁵ reported an RCT comparing milk SLIT with OIT. After therapy, 1 of 10 subjects in the SLIT group and 14 of 20 subjects in the OIT group passed an 8-g OFC ($P = .002$). With regard to safety, the overall reaction rate was similar between SLIT and OIT (29% vs 23%), but reactions with OIT were more likely to include respiratory, gastrointestinal, or systemic reactions, with increased need for rescue medications. They concluded that although OIT is more efficacious, it also carries a greater risk of systemic side effects.

More recently, Narisety et al³¹ reported a DBPC trial comparing peanut SLIT and OIT. Doses were escalated to 3.7 mg (SLIT) or 2000 mg (OIT), and subjects were rechallenged after 6 and 12 months of maintenance. After unblinding, therapy was modified per protocol to offer an additional 6 months of therapy. Subjects passing OFCs at 12 or 18 months were taken off treatment for 4 weeks and rechallenged. Only 16 of 21 subjects completed the 12-month double-blind phase, and all had a greater than 10-fold increase in challenge threshold. However, the threshold was significantly greater in the OIT group compared with that in the SLIT group (141- vs 22-fold). Adverse reactions were more common with OIT, including moderate reactions, doses requiring medication, and study discontinuation secondary to gastrointestinal symptoms. SU was found in only 4 subjects at study completion.

EPIT

EPIT uses novel delivery of allergen to the skin through application of an allergen-containing patch designed to activate skin Langerhans cells with subsequent systemic downregulation

of effector cell responses.^{75,76} Many preclinical studies have demonstrated these mechanistic pathways and the potential for clinical efficacy. For example, mice sensitized to ovalbumin, peanut, or aeroallergens were allocated to EPIT, SCIT, and untreated and negative control groups.⁷⁷ After 8 weeks of weekly treatment, allergen challenge showed decreased airway hyperreactivity with EPIT at levels similar to those seen in the SCIT group. Levels of specific IgG_{2a} for all allergens increased with EPIT similar to those in SCIT, whereas the IgE/IgG_{2a} ratio decreased.

The only published clinical trial using EPIT was a DBPC study of 18 children with milk allergy who were treated for 3 months.⁷⁸ Adverse events were common, occurring in a majority of actively treated subjects, but were confined to local erythema or eczema at application sites. The OFC threshold after 3 months of treatment showed some evidence of desensitization, although the differences were not statistically significant. Additional phase 1 and 2 studies of peanut EPIT have now been conducted, and although the results have only been published in abstract form, they have been sufficiently encouraging to lead to an active clinical development program in Europe and North America, with a phase 3 study now underway. In addition, EPIT is also being developed for the potential treatment of other food allergies, with a phase I/II milk trial currently ongoing.

MODIFIED ALLERGEN IMMUNOTHERAPY

Theoretically, immunotherapy with proteins that are altered such that IgE-binding epitopes are removed or significantly altered while maintaining relevant T-cell binding could provide similar efficacy to the unmodified protein with improved safety. If successful, these approaches could potentially induce desensitization with far shorter courses of therapy by safely providing higher doses of the tolerogenic epitopes with less need for gradual dose escalation. Two general approaches are under investigation, one relying on modification of IgE-binding sites to reduce reactivity and the second based on identification of specific tolerogenic epitopes that are spliced from the larger molecule and provided as “peptide immunotherapy.” The latter approach is now in phase III trials for cat allergen^{79,80} and is being actively pursued in preclinical trials with food allergens.^{81,82}

The second approach, based on the disruption of IgE-binding sites, has been applied to peanut with the development of a recombinant vaccine in which the IgE-binding epitopes of Ara h 1, 2, and 3 were modified by single amino acid substitutions and then encapsulated in inactivated *Escherichia coli*. In mouse models the modified allergen did not bind IgE and reduced allergic symptoms on rechallenge.^{83,84} However, a phase I trial with this product, EMP-123, which is administered per rectum, were disappointing.⁸⁵ In fact, acute allergic reactions were so common that 5 of 10 subjects were unable to complete dosing, indicating that IgE binding was not adequately reduced by using this modification.

POTENTIAL ROLE FOR ADJUNCTIVE THERAPIES

Several potential adjunctive therapies to OIT have been studied. Thus far, most have been directed at improving safety, but the ideal therapy would improve both safety and efficacy. Omalizumab was first studied as an adjunct to SCIT, demonstrating significant reductions in adverse reactions.^{86,87} The potential role of omalizumab with OIT was first studied in a pilot study of 11 subjects with milk allergy.⁸⁸ OIT was rapidly

escalated to 2000 mg over 7 to 11 weeks, and among 2301 doses, 41 were associated with reactions, with 71% mild and 10% severe. A second open-label pilot study used omalizumab with peanut OIT,⁸⁹ with 12 of 13 subjects successfully escalating to 4000 mg in a median of 8 weeks and only 2% of doses precipitating adverse reactions, although 1 subject withdrew because of gastrointestinal symptoms.

The first DBPC trial of omalizumab and OIT was recently published in a study of 57 subjects with severe milk allergy and including measures of both desensitization and SU.⁴¹ The study demonstrated significant improvements in all safety end points, as well as the time needed to achieve maintenance, but there were no differences in any measure of efficacy, including immunologic biomarkers or rates of desensitization or SU. Other medications that have been suggested to reduce adverse reactions include ketotifen and leukotriene receptor antagonists,^{90,91} and as noted, H₁ and H₂ antagonists are commonly used with apparent benefit but have not been formally studied.

Other adjunctive therapies under consideration are focused more on their potential adjuvant effects. A DBPC trial of *Lactobacillus rhamnosus* and peanut OIT suggested that the coadministration of this probiotic might facilitate the induction of SU; however, the study did not include a group receiving OIT without probiotics for comparison.⁹² Other potential immunomodulatory approaches include IFN- γ ,⁹³ Chinese herbs,⁹⁴ T_H1-promoting adjuvants,⁹⁵ and mAbs directed against pathways associated with T_H2-mediated inflammation.⁹⁶ Although it is possible that any of these approaches alone could be effective in the treatment of FA, combining them with allergen-specific immunotherapy has a far greater chance of making a real difference in efficacy while potentially improving safety by both directly reducing adverse reactions and allowing the use of lower doses of the food allergen, shorter courses of therapy, or both.

WHAT IS THE OPTIMAL TREATMENT RESPONSE?

With phase III studies of both OIT and EPIT now underway, it is likely that we will have 1 or more approved treatment options for peanut allergy in the next 5 years, with therapies for other foods to follow. Although further study is needed, it is likely that EPIT only induces a modest level of desensitization, and the OIT protocols under current study are using relatively low maintenance doses, such that the degree of desensitization might not be as robust as that seen with some of the studies reviewed above. Therefore it is likely that the first approved treatments will provide more modest levels of protection than many had hoped, and because this field moves forward, there needs to be an ongoing dialogue regarding the optimal goals of treatment.

Clearly, safety should remain the pre-eminent driving force. With regard to efficacy, very different goals emerge in discussions with patients, families, and practitioners. Although everyone would like to see a cure, this is clearly not in the realm of possibility with the therapies currently under study. Short of that, the goal could range from a low level of protection that could reduce the risk with small accidental exposures to complete reintroduction of the food into the diet. In the end, it is likely that these goals will differ between patients and even moreso between foods. For example, most patients with peanut and tree nut allergy tell me that they will be satisfied with that low level of protection, whereas most with milk and egg allergy hope that treatment will allow for introduction of the food into the diet, at least in the

baked form. All of these issues will require careful thought and discussion, with the reality in the end being driven by the safety and potential efficacy of the therapies as they emerge.

THE SEARCH FOR BIOMARKERS

The clinical application of food immunotherapy would benefit greatly from identification of biomarkers that could predict both risks and responses to therapy on an individual basis. Although the immunologic changes described above, including IgE and IgG₄ measurements, skin tests, and basophil activation, correspond to overall outcomes, they are quite inconsistent with regard to individual responses. Especially for OIT, it would be ideal if we could identify pretreatment characteristics that could predict those subjects at higher risk of reactions, those who might most benefit from cotreatment with omalizumab or other agents, or those who might be able to escalate through treatment more rapidly. For all treatments, there would be tremendous value in posttreatment biomarkers that could identify those subjects with more robust responses, those who might need an extra year or 2 of treatment, those with SU, and, even more importantly, those at higher risk of losing protection with even brief lapses in exposure. These biomarkers will be even more important when these treatments are in clinical practice because pretreatment and posttreatment OFCs will not likely be routine. Hopefully, the larger studies that are now underway will reveal more consistent patterns than were not seen in the smaller studies to date (eg, pretreatment IgE level or posttreatment IgG₄/IgE ratio).

SUMMARY AND CONCLUSIONS

The studies presented in this review demonstrate that at least some degree of desensitization can be achieved in most patients with both OIT and SLIT and possibly EPIT. Whereas OIT appears to induce a far greater degree of desensitization and chance of achieving SU, it is accompanied by an increased risk of both systemic reactions and intolerable gastrointestinal symptoms. Furthermore, even with OIT, SU has only been seen in a minority of subjects in every study in which this has been evaluated.

These recent advances have given both patients and practitioners hope that these treatments are now ready for clinical use. In fact, even though there are no FDA-approved products, both OIT and SLIT are being used increasingly in practice settings, which is only possible because the products needed for OIT can be purchased in the grocery store.⁹⁷ Personally, I firmly believe that many issues need to be addressed before food immunotherapy should be used in clinical practice.⁹⁸ Systemic reactions occur unpredictably during and after treatment, and at present, it appears that OIT actually increases the risk of systemic reactions compared with practicing avoidance. It is also unclear whether food immunotherapy, which requires frequent visits and close follow-up, is cost-effective compared with food avoidance or even whether long-term quality of life will be significantly improved.

Finally, little is known about the optimal duration or long-term efficacy of these therapies, potentially leaving treated patients at high risk of subsequent reactions with even brief lapses in exposure. In fact, it appears likely that any of these treatments will need to be continued indefinitely to maintain protection. This raises additional concerns about long-term adherence, which has been consistently poor with other forms of immunotherapy⁹⁹ and

was clearly shown to be the case in the 3 year follow-up study of peanut SLIT.⁷³

Thus although these therapies are promising, further research to optimize therapy and reduce risk is clearly needed. Even more importantly, research seeking to develop new and better treatments will be critically important. I do not know what food immunotherapy will be like 20 to 30 years from now, but I am hopeful that it will look nothing like the therapies described in this review. These will be exciting times that might eventually allow us to use words like tolerance and cure in treating patients with severe persistent FA.

What do we know?

- OIT and SLIT can induce allergen-specific desensitization to common food allergens.
- The magnitude of desensitization is far greater with OIT, but OIT also carries a higher risk of significant side effects.
- Desensitization is transient in most patients, so that continued exposure to the food antigen is needed to maintain protection.
- Ten percent to 20% of patients are unable to tolerate OIT, most often because of intolerable gastrointestinal side effects.
- Immunologic changes consistent with desensitization are evident, although there is significant individual variability, and none of these changes appear sufficient to serve as an accurate biomarker to predict either the risk or response to treatment.

What is still unknown?

- Although it appears that EPIT can induce some level of desensitization, the magnitude and durability of that response is unknown.
- The long-term outcomes of these treatments are largely unknown, including the overall risk/benefit ratio and cost-effectiveness.
- Although the short-term prospects for food immunotherapy are becoming clear, the field might look vastly different in the next 20 years.

REFERENCES

1. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol* 2011;127:594-602.
2. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128:e9-17.
3. Boyce JA, Assa'a A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-Sponsored Expert Panel Report. *Nutrition* 2011;27:253-67.
4. Sampson HA, Aceves S, Bock SA, James J, Jones S, Lang D, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol* 2014;134:1016-25.e43.
5. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson HA. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010;125:1322-6.
6. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2007;120:1172-7.
7. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. *J Allergy Clin Immunol* 2007;120:1413-7.
8. Sicherer SH, Noone SA, Munoz-Furlong A. The impact of childhood food allergy on quality of life. *Ann Allergy Asthma Immunol* 2001;87:461-4.
9. Robbins KA, Wood RA, Keet CA. Milk allergy is associated with decreased growth in US children. *J Allergy Clin Immunol* 2014;134:1466-8.e6.
10. Atkins D, Bock SA. Fatal anaphylaxis to foods: epidemiology, recognition, and prevention. *Curr Allergy Asthma Rep* 2009;9:179-85.
11. Fleischer DM, Perry TT, Atkins D, Wood RA, Burks AW, Jones SM, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. *Pediatrics* 2012;130:e25-32.
12. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol* 2014;133:621-31.
13. Keet CA, Wood RA. Emerging therapies for food allergy. *J Clin Invest* 2014;124:1880-6.
14. Berin MC, Sicherer S. Food allergy: mechanisms and therapeutics. *Curr Opin Immunol* 2011;23:794-800.
15. Berin MC. Future therapies for IgE-mediated food allergy. *Curr Pediatr Rep* 2014;2:119-26.
16. Edwards HE. Oral desensitization in food allergy. *Can Med Assoc J* 1940;43:234-6.
17. Bauer A, Ekanayake Mudiyanse S, Wigger-Alberti W, Elsner P. Oral rush desensitization to milk. *Allergy* 1999;54:894-5.
18. Patriarca G, Schiavino D, Nucera E, Schinco G, Milani A, Gasbarrini GB. Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology* 1998;45:52-8.
19. Patriarca C, Romano A, Venuti A, Schiavino D, Di Rienzo V, Nucera E, et al. Oral specific hyposensitization in the management of patients allergic to food. *Allergol Immunopathol (Madr)* 1984;12:275-81.
20. Potemkina AM, Timerbaeva GM. [Specific desensitization treatment of children with food hypersensitivity by the sublingual method]. *Pediatr* 1982;2:38-40.
21. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. *J Allergy Clin Immunol* 2005;116:1073-9.
22. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992;90:256-62.
23. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol* 2009;124:286-91, e1-6.
24. Jones SM, Burks AW, Dupont C. State of the art on food allergen immunotherapy: oral, sublingual, and epicutaneous. *J Allergy Clin Immunol* 2014;133:318-23.
25. Keet CA, Frischmeyer-Guerrero PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2012;129:448-55, e1-5.
26. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012;367:233-43.
27. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol* 2011;127:654-60.
28. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. *J Allergy Clin Immunol* 2014;133:468-75.
29. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009;124:292-300, e1-7.
30. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschoner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010;126:83-91.e1.
31. Narisety SD, Frischmeyer-Guerrero PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. *J Allergy Clin Immunol* 2015;135:1275-82.
32. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy* 2011;41:1273-81.
33. Anagnostou K, Islam S, King Y, Islam S, Deighton J, Ewan P. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet* 2014;383:1297-304.

34. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007;119:199-205.
35. Vickery BP, Pons L, Kulis M, Steele P, Jones SM, Burks AW. Individualized IgE-based dosing of egg oral immunotherapy and the development of tolerance. *Ann Allergy Asthma Immunol* 2010;105:444-50.
36. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 2004;59:980-7.
37. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol* 2008;121:343-7.
38. Skripak JM, Nash SD, Rowley H, Breerton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008;122:1154-60.
39. Martorell A, De la Hoz B, Ibanez MD, Bone J, Terrados MS, Michavila A, et al. Oral desensitization as a useful treatment in 2-year-old children with cow's milk allergy. *Clin Exp Allergy* 2011;41:1297-304.
40. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol* 2010;105:376-81.
41. Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol* 2016;137:1103-10.
42. Syed A, Garcia MA, Lyu SC, Bucayu R, Kohli A, Ishida S, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol* 2014;133:500-10.
43. Staden U, Rolinck-Werninghaus C, Brewe F, Wahn U, Niggemann B, Beyer K. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 2007;62:1261-9.
44. Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2013;132:737-9.e6.
45. Gorelik M, Narisety SD, Guerrero AL, Chichester KL, Keet CA, Bieneman AP, et al. Suppression of the immunologic response to peanut during immunotherapy is often transient. *J Allergy Clin Immunol* 2015;135:1283-92.
46. Caminiti L, Pajno GB, Crisafulli G, Chiera F, Collura M, Panasci G, et al. Oral immunotherapy for egg allergy: a double-blind placebo-controlled study, with postdesensitization follow-up. *J Allergy Clin Immunol Pract* 2015;3:532-9.
47. Vickery BP, Lin J, Kulis M, Fu Z, Steele PH, Jones SM, et al. Peanut oral immunotherapy modifies IgE and IgG4 responses to major peanut allergens. *J Allergy Clin Immunol* 2013;131:128-34, e1-3.
48. Patriarca G, Nucera E, Pollastrini E, De Pasquale T, Lombardo C, Buonomo A, et al. Oral rush desensitization in peanut allergy: a case report. *Dig Dis Sci* 2006;51:471-3.
49. Mansfield L. Successful oral desensitization for systemic peanut allergy. *Ann Allergy Asthma Immunol* 2006;97:266-7.
50. Patriarca G, Nucera E, Roncallo C, Pollastrini E, Bartolozzi F, De Pasquale T, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003;17:459-65.
51. Morisset M, Moneret-Vautrin DA, Guenard L, Cuny JM, Frentz P, Hatahet R, et al. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. *Eur Ann Allergy Clin Immunol* 2007;39:12-9.
52. Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. *Pediatr Allergy Immunol* 2013;24:75-83.
53. Itoh N, Itagaki Y, Kurihara K. Rush specific oral tolerance induction in school-age children with severe egg allergy: one year follow up. *Allergol Int* 2010;59:43-51.
54. Dello Iacono I, Tripodi S, Calvani M, Panetta V, Verga MC, Miceli Sopo S. Specific oral tolerance induction with raw hen's egg in children with very severe egg allergy: a randomized controlled trial. *Pediatr Allergy Immunol* 2013;24:66-74.
55. Garcia Rodriguez R, Urra JM, Feo-Brito F, Galindo PA, Borja J, Gomez E, et al. Oral rush desensitization to egg: efficacy and safety. *Clin Exp Allergy* 2011;41:1289-96.
56. Zapatero L, Alonso E, Fuentes V, Martinez MI. Oral desensitization in children with cow's milk allergy. *J Investig Allergol Clin Immunol* 2008;18:389-96.
57. Alvaro M, Giner MT, Vazquez M, Lozano J, Dominguez O, Piquer M, et al. Specific oral desensitization in children with IgE-mediated cow's milk allergy. Evolution in one year. *Eur J Pediatr* 2012;171:1389-95.
58. Sanchez-Garcia S, Rodriguez del Rio P, Escudero C, Garcia-Fernandez C, Ramirez A, Ibanez MD. Efficacy of oral immunotherapy protocol for specific oral tolerance induction in children with cow's milk allergy. *Isr Med Assoc J* 2012;14:43-7.
59. Narisety SD, Skripak JM, Steele P, Hamilton RG, Matsui EC, Burks AW, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2009;124:610-2.
60. Begin P, Winterroth LC, Dominguez T, Wilson SP, Bacal L, Mehrotra A, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. *Allergy Asthma Clin Immunol* 2014;10:1.
61. Begin P, Dominguez T, Wilson SP, Bacal L, Mehrotra A, Kausch B, et al. Phase I results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. *Allergy Asthma Clin Immunol* 2014;10:7.
62. Wasserman RL, Factor JM, Baker JW, Mansfield LE, Katz Y, Hague AR, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. *J Allergy Clin Immunol Pract* 2014;2:91-6.
63. Sanchez-Garcia S, Rodriguez Del Rio P, Escudero C, Martinez-Gomez MJ, Ibanez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. *J Allergy Clin Immunol* 2012;129:1155-7.
64. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. *Ann Allergy Asthma Immunol* 2011;106:73-4.
65. Meglio P, Giampietro PG, Gianni S, Galli E. Oral desensitization in children with immunoglobulin E-mediated cow's milk allergy—follow-up at 4 yr and 8 months. *Pediatr Allergy Immunol* 2008;19:412-9.
66. Yeung JP, Kloda LA, McDevitt J, Ben-Shoshan M, Alizadehfar R. Oral immunotherapy for milk allergy. *Cochrane Database Syst Rev* 2012;11:CD009542.
67. Brozek JL, Terracciano L, Hsu J, Kreis J, Compalati E, Santesso N, et al. Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. *Clin Exp Allergy* 2012;42:363-74.
68. Nurmatov U, Devereux G, Worth A, Healy L, Sheikh A. Effectiveness and safety of orally administered immunotherapy for food allergies: a systematic review and meta-analysis. *Br J Nutr* 2014;111:12-22.
69. Akdis CA, Barlan IB, Bahecciler N, Akdis M. Immunological mechanisms of sublingual immunotherapy. *Allergy* 2006;61(suppl 81):11-4.
70. Untersmayr E, Jensen-Jarolim E. The role of protein digestibility and antacids on food allergy outcomes. *J Allergy Clin Immunol* 2008;121:1301-10.
71. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2011;127:640-6.e1.
72. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. *J Allergy Clin Immunol* 2013;131:119-27, e1-7.
73. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, et al. Sublingual immunotherapy for peanut allergy: Long-term follow-up of a randomized multicenter trial. *J Allergy Clin Immunol* 2015;135:1240-8, e1-3.
74. Chin SJ, Vickery BP, Kulis MD, Kim EH, Varshney P, Steele P, et al. Sublingual versus oral immunotherapy for peanut-allergic children: a retrospective comparison. *J Allergy Clin Immunol* 2013;132:476-8.e2.
75. Dioszeghy V, Mondoulet L, Dhelft V, Ligouis M, Puteaux E, Dupont C, et al. The regulatory T cells induction by epicutaneous immunotherapy is sustained and mediates long-term protection from eosinophilic disorders in peanut-sensitized mice. *Clin Exp Allergy* 2014;44:867-81.
76. Mondoulet L, Dioszeghy V, Thebault C, Benhamou PH, Dupont C. Epicutaneous immunotherapy for food allergy as a novel pathway for oral tolerance induction. *Immunotherapy* 2015;7:1293-305.
77. Mondoulet L, Dioszeghy V, Ligouis M, Dhelft V, Dupont C, Benhamou PH. Epicutaneous immunotherapy on intact skin using a new delivery system in a murine model of allergy. *Clin Exp Allergy* 2010;40:659-67.
78. Dupont C, Kalach N, Soulaire P, Legoue-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. *J Allergy Clin Immunol* 2010;125:1165-7.
79. Patel D, Couroux P, Hickey P, Salapatek AM, Laidler P, Larche M, et al. Fel d 1-derived peptide antigen desensitization shows a persistent treatment effect 1 year after the start of dosing: a randomized, placebo-controlled study. *J Allergy Clin Immunol* 2013;131:103-9, e1-7.
80. Worm M, Lee HH, Kleine-Tebbe J, Hafner RP, Laidler P, Healey D, et al. Development and preliminary clinical evaluation of a peptide immunotherapy vaccine for cat allergy. *J Allergy Clin Immunol* 2011;127:89-97, e1-14.
81. Yang M, Yang C, Mine Y. Multiple T cell epitope peptides suppress allergic responses in an egg allergy mouse model by the elicitation of forkhead box

- transcription factor 3- and transforming growth factor-beta-associated mechanisms. *Clin Exp Allergy* 2010;40:668-78.
82. Swoboda I, Balic N, Klug C, Focke M, Weber M, Spitzauer S, et al. A general strategy for the generation of hypoallergenic molecules for the immunotherapy of fish allergy. *J Allergy Clin Immunol* 2013;132:979-81.
 83. Prickett SR, Voskamp AL, Phan T, Dacumos-Hill A, Mannering SI, Rolland JM, et al. Ara h 1 CD4+ T cell epitope-based peptides: candidates for a peanut allergy therapeutic. *Clin Exp Allergy* 2013;43:684-97.
 84. Li XM, Srivastava K, Huleatt JW, Bottomly K, Burks AW, Sampson HA. Engineered recombinant peanut protein and heat-killed *Listeria monocytogenes* coadministration protects against peanut-induced anaphylaxis in a murine model. *J Immunol* 2003;170:3289-95.
 85. Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, et al. A phase 1 study of heat/phenol-killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. *Allergy* 2013;68:803-8.
 86. Casale TB, Busse WW, Kline JN, Ballas ZK, Moss MH, Townley RG, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. *J Allergy Clin Immunol* 2006;117:134-40.
 87. Massanari M, Nelson H, Casale T, Busse W, Kianifard F, Geba GP, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in allergic asthma. *J Allergy Clin Immunol* 2010;125:383-9.
 88. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. *J Allergy Clin Immunol* 2011;127:1622-4.
 89. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. *J Allergy Clin Immunol* 2013;132:1368-74.
 90. Takahashi M, Taniuchi S, Soejima K, Sudo K, Hatano Y, Kaneko K. New efficacy of LTRAs (montelukast sodium): it possibly prevents food-induced abdominal symptoms during oral immunotherapy. *Allergy Asthma Clin Immunol* 2014;10:3.
 91. Jagdis A, Berlin N, Barron C, Giruparajah M, Leader N, Maclachlan S, et al. Effect of ketotifen premedication on adverse reactions during peanut oral immunotherapy. *Allergy Asthma Clin Immunol* 2014;10:36.
 92. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. *J Allergy Clin Immunol* 2015;135:737-44.e8.
 93. Noh G, Lee SS. A pilot study of interferon-gamma-induced specific oral tolerance induction (ISOTI) for immunoglobulin E-mediated anaphylactic food allergy. *J Interferon Cytokine Res* 2009;29:667-75.
 94. Wang J, Patil SP, Yang N, Ko J, Lee J, Noone S, et al. Safety, tolerability, and immunologic effects of a food allergy herbal formula in food allergic individuals: a randomized, double-blinded, placebo-controlled, dose escalation, phase 1 study. *Ann Allergy Asthma Immunol* 2010;105:75-84.
 95. Beeh KM, Kanniss F, Wagner F, Schilder C, Naudts I, Hammann-Haenni A, et al. The novel TLR-9 agonist QbG10 shows clinical efficacy in persistent allergic asthma. *J Allergy Clin Immunol* 2013;131:866-74.
 96. Pelaia G, Vatrella A, Maselli R. The potential of biologics for the treatment of asthma. *Nat Rev Drug Discov* 2012;11:958-72.
 97. Traister RS, Green TD, Mitchell L, Greenhawt M. Community opinions regarding oral immunotherapy for food allergies. *Ann Allergy Asthma Immunol* 2012;109:319-23.
 98. Wood RA, Sampson HA. Oral immunotherapy for the treatment of peanut allergy: is it ready for prime time? *J Allergy Clin Immunol Pract* 2014;2:97-8.
 99. Cox LS, Hankin C, Lockey R. Allergy immunotherapy adherence and delivery route: location does not matter. *J Allergy Clin Immunol Pract* 2014;2:156-60.