Treatment for food allergy

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Activity Objectives:

1. To understand the relative advantages and drawbacks of each of the 3 main forms of immunotherapy for food allergy (oral immunotherapy [OIT], sublingual immunotherapy [SLIT], and epicutaneous immunotherapy [EPIT]).
2. To become familiar with the general protocol design for the different forms of food allergy immunotherapy.
3. To know the difference in the commonly used terms in food allergy treatment: desensitization, sustained unresponsiveness, oral tolerance, and remission.

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The prevalence of IgE-mediated food allergy is an increasing public health concern effecting millions of persons worldwide. The current standard of treatment is strict avoidance of the offending food or foods, and to date, there are no regulatory approved treatments for food allergy. A significant amount of research has been directed at various forms of food immunotherapy, including oral, sublingual, and epicutaneous delivery routes. Although oral immunotherapy has shown the greatest promise for efficacy in terms of the amount of protein that can be ingested, it has also demonstrated less tolerability and a less favorable safety profile compared with sublingual immunotherapy and epicutaneous immunotherapy, which offers

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the least protection but has the best safety and tolerability profile. Studies have been conducted with adding adjuvants and anti-IgE to enhance either the efficacy or safety of food immunotherapy. Multiple concepts of food immunotherapy beyond these first-generation treatments are in either animal or early phase 1 studies. (J Allergy Clin Immunol 2018;141:1-9.)

Key words: *Food allergy, food immunotherapy, oral immunotherapy, sublingual immunotherapy, epicutaneous immunotherapy*

Abbreviations used
EPIT: Epicutaneous immunotherapy
OFC: Oral food challenge
OIT: Oral immunotherapy
SLIT: Sublingual immunotherapy
SU: Sustained unresponsiveness

IgE-mediated food allergy is a global health problem that affects millions of persons and every aspect of the life of a patient with food allergy.[1,2] In the United States food allergy affects 15 million Americans, including 5.9 million children less than 18 years old, with epidemiologic studies demonstrating an increasing prevalence in the last 2 decades.[2]

Food allergy results from a breakdown of oral tolerance, delayed development of oral tolerance, or both in subjects genetically and possibly environmentally predisposed to atopic disease.[3,4] Although a large number of foods have been reported to cause allergic reactions, milk, egg, and peanuts are the 3 most common food allergens in the United States.[1] The rising tide of food allergy provides considerable motivation and directs resources toward finding a treatment and eventual cure.

Currently, recommended management of food allergy requires strict and careful food avoidance.[5] Treatment of accidental ingestions with an epinephrine autoinjector is anxiety provoking and perceived by patients and families as challenging.[6] Hence the quality of life for patients and their families is significantly affected.[7]

An understanding of the definitions of clinical desensitization, sustained unresponsiveness (SU; remission), and oral tolerance are essential to evaluate emerging therapies for food allergy (Table I).[8] Desensitization is defined as an increase in reaction threshold to a food allergen while receiving active therapy and might equate to protection from accidental ingestion. Desensitization can often be achieved after months of therapy and importantly only continues during the therapy. SU is defined as a lack of clinical reaction to a food allergen after active therapy has been discontinued for a period of time. Currently, it is thought that SU requires some level of continued allergen exposure to sustain the unresponsive state. Achievement of SU requires several years of therapy and has been seen in only subsets of treated subjects. This loss of tolerance after immunotherapy is not unique to food allergy but also occurs after various forms of immunotherapy to airborne environmental allergens and insect sting allergens. Therefore it might be more appropriate to refer to this temporary state of nonresponsiveness off therapy as "remission," as traditionally done with autoimmune disorders. Oral tolerance is a term used to describe a complete lack of clinical reactivity to an ingested food allergen, typically as a natural occurrence; this state of clinical tolerance is not thought to depend on continued food allergen exposure.[3,4] The development of true immunologic and clinical tolerance after active immunotherapy for food allergy has not been defined by current clinical trials to date. This point is essential to understanding the clinical outcomes and potential future implications for food allergen immunotherapy. Several types of immunotherapy, including oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT), are under active investigation for the treatment of food allergy (Fig 1).

OIT

OIT has been explored as a viable treatment option for food allergy in the past and more recently for more than a decade. A variety of food allergens have been studied, but most randomized controlled trials have focused on peanut, milk, and egg.[9-21] This form of immunotherapy requires daily ingestion of an allergen powder (eg, contains peanut protein along with lipids and carbohydrates) that is mixed with another food and ingested. OIT involves treating patients with escalating doses of the offending food, with the hope of slowly inducing desensitization or possibly SU. The postulated mechanism of action of immunotherapy involves modulation of the immune response, including transition from allergen-specific IgE to IgG_4 and decreased basophil activation to allergen cross-linking, with an increase in numbers of regulatory T cells.[22-25] OIT has been associated with the most robust clinical and immunologic outcome of any of the treatment options, including findings of desensitization and in some cases SU, as well as significant immunomodulation.

Peanut OIT

Peanut OIT (Table II)[9,10,15-17,26-28] was first reported in a trial in the United States in 2009.[26] In one of the first studies on peanut allergy,[26] children with this allergy underwent an OIT protocol, including initial-day escalation, buildup and maintenance phases, and then oral food challenges (OFCs) to examine the desensitization effect. Of 29 subjects who completed the protocol, 27 ingested 3900 mg of peanut protein (equivalent to about 16 peanuts) after treatment. Skin prick test reactivity, peanut-specific IgE levels, and basophil activation diminished significantly in the treatment group, whereas peanut-specific IgG_4 levels increased significantly.

A randomized controlled trial examining peanut OIT was reported, including 28 subjects aged 1 to 16 years.[17] Of 16 children in the treatment group, all tolerated 5000 mg of peanut protein (roughly 20 peanuts) versus none in the placebo-treated group. Treated subjects had significantly reduced skin prick test reactivity, lower IL-5 and IL-13 levels, increased peanut-specific IgG_4 levels, and no significant change in peanut-specific IgE levels at the time of the OFC.

The Study of induction of Tolerance to Oral Peanut (STOP) II trial was a randomized controlled crossover trial studying children 7 to 16 years of age.[9] The primary outcome, desensitization (defined as tolerating 1400 mg of peanut protein), was recorded for 62% of subjects.

Although it has become clear that desensitization is possible using OIT, a significant remaining question is whether, on

TABLE I. Definitions of clinical desensitization, SU, remission, and oral tolerance

Desensitization	Defined as an increase in reaction threshold to a food allergen while receiving active therapy and might equate to protection from accidental ingestion. Often, desensitization can be achieved after months of therapy and importantly only continues during therapy.
SU	Defined as a lack of clinical reaction to a food allergen after active therapy has been discontinued for a period of time. Currently, it is thought that SU requires some level of continued allergen exposure to sustain the unresponsive state.
Remission	Defined as a temporary state of nonresponsiveness off therapy after immunotherapy and might be a better term for allergy immunotherapy than SU. Loss of clinical reactions after various forms of immunotherapy occurs in food allergy immunotherapy, as well as immunotherapy for airborne environmental allergens and insect sting allergens.
Oral tolerance	Defined as a complete lack of clinical reactivity to an ingested food allergen, typically as a natural occurrence. This state of clinical tolerance is not thought to depend on continued food allergen exposure.

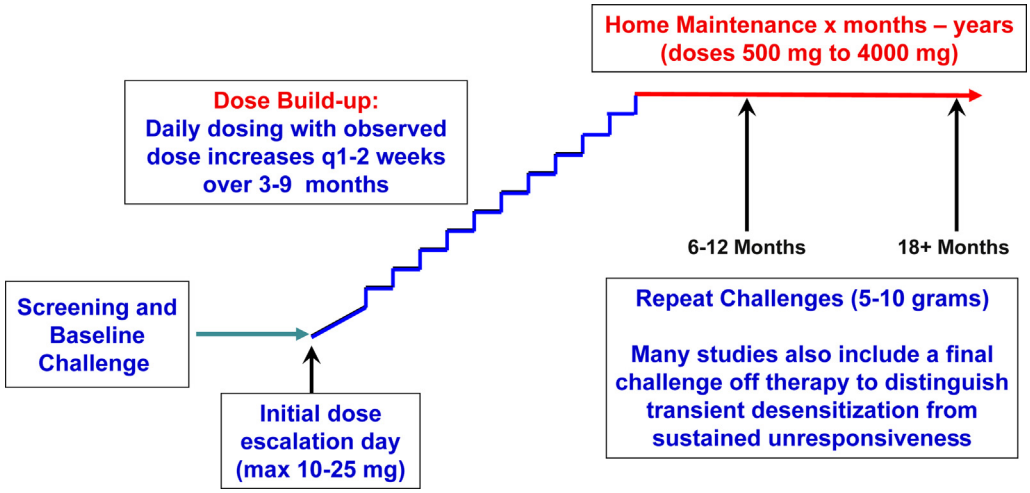

FIG 1. Typical schematic for food immunotherapy, with initial dosing, dose build-up, and maintenance therapy. Adapted from Wood.[18]

discontinuation of OIT, the patient will exhibit SU for extended periods of time to peanut protein. Another trial examined the characteristics of patients who exhibited SU. In this trial 12 of 24 subjects demonstrated SU at a 5000-mg OFC 1 month after discontinuing OIT.[17] Those exhibiting SU had lower levels at baseline and, at the final OFC, had lower skin prick test response size and peanut-specific IgE, Ara h 1, and Ara h 2 levels and reduced peanut-specific IgE/total IgE ratios. No significant difference in peanut-specific IgG_4 levels was found. The diet was liberalized to incorporate peanut in patients exhibiting SU.

A more recent study tested the safety, effectiveness, and feasibility of early OIT in the treatment of peanut allergy.[16] Outcomes were compared with those of 154 matched standard-care control subjects. Overall, after treatment for a median of 29 months, 29 (78%) of 37 in the intent-to-treat analysis achieved SU (for 4 months). Per-protocol, the overall proportion achieving SU was 29 (91%) of 32. In this study peanut-specific IgE levels decreased significantly in children treated with early OIT, who were 19-fold more likely to successfully consume dietary peanut than matched standard-care control subjects, in whom peanut-specific IgE levels increased significantly.

Peanut OIT with adjuvant

A study of peanut OIT used a combination of OIT and a bacterial adjuvant.[29] In this double-blind, randomized, placebo-controlled trial, the probiotic *Lactobacillus* and peanut OIT were delivered to patients 1 to 10 years old. After a maintenance does of 2 g of peanut, desensitization occurred to an OFC dose of 4 g in 89% of patients. Possible SU was reported only 2 to 5 weeks after discontinuation of treatment in 23 (82.1%) of 28 patients and in 1 of 28 patients receiving placebo. The limitations of this study include a lack of an OIT-only group to show the effect of the probiotic and the short time off of OIT until challenge. Parental acceptance of this treatment was high.[30]

Egg OIT

For more information on egg OIT, see Table III.[11,12,31,32] In an initial randomized trial of egg OIT,[11] of 40 children receiving egg OIT, after a maintenance dose of 2 g, 55% were desensitized to a 5-g egg white powder OFC at 10 months, and 75% were desensitized to a 10-g egg white powder OFC at 22 months. Of those patients desensitized, which was confirmed by a 10-g OFC, 28% exhibited SU 8 weeks later. Those patients who exhibited SU passed a 10-g egg powder OFC and were fed a whole cooked egg an hour later. A follow-up to this original study showed 50% of the original patients with egg allergy had SU after 4 years of treatment.[33]

Another randomized controlled study reported a 4-month desensitization protocol to a maintenance dose of 4 g of egg white powder, followed by egg avoidance to examine SU.[19] Among 16 children aged 4 to 11 years who achieved desensitization, 31% achieved SU after 3 months of avoidance. Those subjects were then fed a cooked or boiled egg on a regular basis.

TABLE II. Peanut OIT studies

Reference	Year	Design	Sample size	Subject age (y)	Maintenance dose (mg)	Duration	Primary outcome
Jones et al[26]	2009	Open label	29	1-16	1800	36 mo	93% Passed 3.9-g peanut OFC
Blumchen et al[10]	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[15]	2011	Randomized, placebo controlled	19	3-11	2000	48 wk	84% Passed 5000-mg peanut OFC
Anagnostou et al[28]	2011	Open label	22	4-18	800	32 wk	64% Tolerated 6.6-g OFC
Anagnostou et al[9]	2014	Randomized, controlled	39	7-16	800	26 wk	62% Tolerated 1400-mg challenge
Vickery et al[17]	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[27]	2014	Randomized, placebo controlled	16	7-13	2000	12 mo	OIT > SLIT in OFC threshold, low rate of SU
Vickery et al[16]	2016	Two dose	40	<4	30; 300	>18 mo	High rate of desensitization

TABLE III. Egg OIT studies

Reference	Year	Design	Sample size	Subject age (y)	Maintenance dose (g)	Duration (mo)	Primary outcome
Buchanan et al[31]	2007	Open label	7	1-16	0.3	24	57% Passed 8-g OFC
Vickery et al[32]	2010	Open label	8	3-13	0.3-3.6	18-50	75% Passed OFC 1 mo after stopping OIT
Burks et al[11]	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
Jones et al[12]	2016	Open label follow-up	40	5-11	1.6	≥60	High rate of egg in diet

Milk OIT

For more information on milk OIT, see Table IV.[14,20,21,34-38] In a recent study of milk OIT,[20] 60 children were randomized to complete an in-hospital rush treatment, followed by a maintenance OIT protocol with a maximum daily dose of 150 mL of cow's milk. After 1 year, 35% of treated children versus 5% of untreated children were able to tolerate a dose of 150 mL of cow's milk.

In another milk OIT trial in a cohort of 60 patients aged 24 to 36 months,[34] 30 children were treated with milk OIT. Of OIT-treated children, 90% became desensitized versus 23% of placebo-treated children.

In a randomized, double-blind, placebo-controlled study of milk OIT, a significant increase was observed in the median cumulative dose tolerated of dry nonfat powdered milk after OIT (5140 mg) compared with placebo (40 mg).[14] Milk IgG_4 levels increased significantly in the active treatment group. This study had more allergic reactions during the study treatment than many, and epinephrine use was not uncommon.

Multifood OIT

Although some children are allergic to only 1 food, others react to many. Multifood OIT has been shown, in a small phase I trial, to be comparable in safety to single-food immunotherapy.[39] In this study 25 subjects allergic to multiple foods were treated with multifood OIT, and 15 subjects allergic to peanut only were treated with peanut only. The dosing of each food was generally 4000 mg. Similar rates of adverse reactions, 3.3% and 3.7%, were observed in each group, most of which were mild. Similar numbers of patients in each group achieved the same target doses of food, with the multifood group taking longer by design, although this was not the primary end point.

Anti-IgE therapy with OIT

A pilot study of omalizumab to facilitate rapid OIT in patients with peanut allergy was performed.[40] This study had no placebo arm, but initial results were promising because rapid OIT in terms of weeks was achieved in 12 of 13 patients. The successfully treated patients were ultimately able to tolerate 4 g of peanut flour in a median time of 8 weeks. The addition of omalizumab to OIT in children with multiple food allergies resulted in 16-week desensitization in 19 of 25 participants.[41] Rapid OIT to milk with omalizumab treatment has also been reported.[42] In this study 9 of 11 patients were desensitized rapidly to 1000 mg in 1 day, although 1 participant dropped out because of abdominal pain and another required epinephrine.

In another double-blind, placebo-controlled trial with milk OIT, subjects were randomized to omalizumab or placebo. Then open-label milk OIT was initiated after 4 months of omalizumab/placebo, with escalation to maintenance over 22 to 40 weeks followed by daily maintenance dosing through month 28.[35] At month 28, omalizumab was discontinued, and subjects passing an OFC continued OIT for 8 weeks, after which OIT was discontinued with rechallenge at month 32 to assess SU. Fifty-seven subjects (7-32 years) were randomized; at month 28, 24 (89%) omalizumab-treated subjects and 20 (71%) placebo-treated

TABLE IV. Milk OIT studies

Reference	Year	Design	Samples size	Subject age (y)	Maintenance dose	Duration	Primary outcome
Meglio et al[37]	2004	Open label	21	6-10	200 mL	6 mo	72% Desensitization to 200 mL of cow's milk daily
Longo et al[20]	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)
Skripak et al[14]	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[38]	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[21]	2010	Randomized, placebo controlled	15	4-10	200 mL	18 wk	67% Tolerant to 200 mL of cow's milk
Martorell et al[34]	2011	Randomized, placebo controlled	30	2-3	200 mL	1 y	90% Showing complete desensitization
Keet et al[36]	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[35]	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

DBPC, Double-blind, placebo-controlled.

subjects passed the 10-g desensitization OFC. At month 32, SU was demonstrated in 48% in the omalizumab group and 36% in the placebo group, which was not significantly different.

In a more recent study,[43] 37 subjects were randomized to omalizumab (n = 29) or placebo (n = 8). After 12 weeks of treatment, subjects underwent a rapid 1-day desensitization of up to 250 mg of peanut protein, followed by weekly increases up to 2000 mg. Omalizumab was then discontinued, and subjects continued on 2000 mg of peanut protein. Subjects underwent an open challenge to 4000 mg of peanut protein 12 weeks after stopping study drug. Subsequently, 23 (79%) of 29 subjects randomized to omalizumab tolerated 2000 mg of peanut protein 6 weeks after stopping omalizumab versus 1 (12%) of 8 receiving placebo ($P < .01$). Twenty-three subjects receiving omalizumab versus 1 subject receiving placebo passed the 4000-mg food challenge.

Dosing strategies in each study have been variable, starting with omalizumab 2 to 4 months before starting OIT, and in other studies omalizumab has been continued throughout OIT dosing. Adverse reactions were reduced markedly during OIT escalation in omalizumab-treated subjects for percentages of doses per subject provoking symptoms, dose-related reactions requiring treatment, and doses required to achieve maintenance.

The updosing frequency of OIT and the number of doses of anti-IgE were variable in each study. In summary, the use of anti-IgE with OIT will allow updosing to proceed more quickly and with fewer allergic side effects. The eventual outcomes of interest, desensitization and SU, have not been shown to be improved by the addition of anti-IgE therapy.

Safety of OIT

OIT is associated with more allergic side effects than other forms of immunotherapy, including induction of episodic anaphylaxis with dosing, dose-limiting gastrointestinal side effects in approximately 20%, and eosinophilic esophagitis in less than 5% of clinical trial participants.[44-46] Dose adjustments are frequently required because of viral illness, exercise, or menses to maintain a safe dosing profile.[10,47] Seasonal allergies can further complicate safety profiles and affect clinical outcomes in those treated with OIT.[48] In a retrospective review including 395 patients, of 240,351 doses, 95 doses required epinephrine administration because of a severe reaction.[49] In that review 298 (85%) patients were able to achieve maintenance dosing. In summary, the very high frequency of significant allergic reactions and gastrointestinal symptoms are limiting factors in the utility of OIT and must be considered when discussing this option as an eventual therapeutic modality.

In summary, OIT has been shown to cause desensitization in most undergoing the therapy, with some subjects achieving SU for short periods of time (weeks to months) but not long-term SU (months to years) without continued ingestion of the allergen in the diet. The balance of allergic side effects versus the benefit of OIT will be an individual decision for each patient and his or her family.

SLIT

SLIT (Table V)[36,50-53] has been evaluated in clinical trials for peanut and a few other foods. This therapy requires application of an allergen extract in the sublingual space (held under the tongue for 2-3 minutes and then swallowed) on a daily basis over the time of treatment. SLIT has been associated with clinical desensitization and moderate immunologic changes.[50,51,54-56] SLIT is well tolerated, with minimal side effects that are typically limited to oropharyngeal itching or tingling. In an initial randomized controlled trial to examine the efficacy of 44 weeks of SLIT in peanut allergy,[52] 14 (70%) of 20 subjects were able to consume either 5 g or at least a

TABLE V. SLIT studies

Reference	Year	Food	Design	Sample size	Subject age (y)	Maintenance dose (mg)	Duration	Primary outcome
Enrique et al[55]	2005	Hazelnut	Randomized, placebo controlled	23	19-53	13.25	8-12 wk	Significant increase in OFC threshold with active SLIT
Kim et al[50]	2011	Peanut	Randomized, placebo controlled	18	2-10	2.5	12 mo	OFC threshold 20 times greater for SLIT vs placebo (median, 1710 vs 85 mg)
Fleischer et al[52]	2012	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[36]	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[27]	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[51]	2015	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

DBPC, Double-blind, placebo-controlled.

TABLE VI. Knowledge gaps and unanswered questions

What is the optimal dose, frequency, and duration of OIT?
Is maintenance therapy required to maintain SU (clinical remission)? If so, at what dose and what frequency?
Does OIT to peanut change quality of life in children with multiple nut allergies?
Is OIT to peanut more appropriate in children who are monoallergic to peanut in contrast to children who are allergic to multiple tree nuts?
Does OIT change risk-taking behavior in patients receiving this treatment, especially with regard to reading labels and dining out?
Is OIT more suitable for some foods than others?
Does OIT to one nut (eg, cashew) cause cross-desensitization to a related nut (eg, pistachio)?

10-fold increase in peanut powder during OFC compared with 15% receiving placebo.

In a retrospective comparison of SLIT with OIT for children with peanut allergy, OIT was found to have more significant changes in peanut-specific IgE and IgG_4 levels.[57] These patients were also 3 times more likely to pass desensitization OFCs when compared with patients undergoing SLIT.

Another study compared peanut SLIT with OIT prospectively in a randomized controlled trial.[27] An increased food challenge threshold was found in both groups but more so with OIT. Specifically, a 141-fold increase in maximum tolerated dose was observed in OIT-treated patients compared with a 22-fold increase in SLIT-treated patients. In addition, greater changes in skin test results and peanut-specific IgE and IgG_4 levels were seen with OIT. However, only a minority of subjects who received OIT or SLIT exhibited SU after 4 weeks of avoidance.

In a multicenter, randomized, double-blind, placebo-controlled trial, a larger study found an acceptable safety profile for SLIT.[51] More than 98% of doses were tolerated without adverse reactions beyond the oropharynx, and no epinephrine was required for symptoms. Further immunologic changes were seen in those with favorable responses by decreased peanut-specific basophil activation and skin prick test results.

For milk SLIT, in an earlier study of 8 patients undergoing 6 months of SLIT, the desensitization rate was 70%, with 4 eventually adding milk to their diet.[53] A randomized controlled trial with 30 children receiving SLIT or SLIT followed by low- or high-dose OIT[36] was done next; subjects were challenged after 12 and 60 weeks of maintenance therapy to 8 g of milk protein. Only 1 of 10 in the SLIT-only group, 6 of 10 in the SLIT and lower-dose OIT group, and 8 of 10 in the SLIT and high-dose OIT group passed the food challenge. This desensitization was not necessarily sustained, with 6 of the 15 desensitized patients regaining reactivity. Of those 6 patients, 2 became reactive after only 1 week. Overall, the addition of OIT led to more desensitization but was also associated with more systemic reactions.

SLIT in general has been shown to offer some modest desensitization without much in the way of SU, but in limited studies, when SLIT is used before OIT, the side effect profile is quite different for OIT. Additionally, the allergic side effects of SLIT have been primarily limited to the oropharynx, with very few systemic symptoms.

EPIT

EPIT has been investigated for the treatment of peanut and milk allergy and involves application of a small allergen patch to the back or upper arm, with patches changed at 24-hour intervals over years of therapy.[33,58,59] EPIT for peanut allergy is associated with clinical desensitization primarily in younger age groups and associated with only modest immunologic changes to date.[33] EPIT is well tolerated, with typically only mild skin irritation noted at the patch site for the majority of those treated.[33,58]

In a pilot study of EPIT, children with milk allergy were randomized to receive a 48-hour patch 3 times per week versus placebo.[58] Ten children received active EPIT for 3 months, and an increasing trend in cumulative tolerated dose of milk from a mean of 1.7 to 23 mL was shown.[60] Adverse events were most common in the skin (reported in 50% of subjects). No episodes of severe reactions or anaphylaxis were reported.

In a multicenter, double-blind, randomized, placebo-controlled study,[33] 74 participants with peanut allergy (age 4-25 years) were treated with Viaskin Peanut 100 μg or Viaskin Peanut 250 μg (DBV Technologies, New York, NY), and 25 were treated with placebo. The primary outcome was treatment success after 52 weeks, which was defined as passing a 5044-mg protein OFC or achieving a 10-fold or greater increase in successfully consumed dose from baseline to week 52. At week 52, treatment success was achieved in 3 (12%) placebo-treated participants, 11 (46%) participants receiving

100 μg, and 12 (48%) participants receiving 250 μg, although no one tolerated the full 5044-mg OFC. Median changes in successfully consumed doses were 0, 43, and 130 mg of protein in the placebo, 100-μg, and 250-μg groups, respectively. Treatment success was higher among younger children (age, 4-11 vs >11 years). Overall, 14% of placebo doses and 80% of 100-μg and 250-μg doses resulted in reactions, predominantly local patch-site and mild reactions. Increases in peanut-specific IgG_4 levels and IgG_4/IgE ratios were observed in peanut EPIT–treated participants, along with trends toward reduced basophil activation and peanut-specific T_H2 cytokine levels.

EPIT remains a subject of much current study, showing some desensitization effect, although less than OIT and SLIT, and an excellent safety profile. However, the precise role for this form of pharmacotherapy in the management of food allergy has yet to be determined.

NON–ALLERGEN-SPECIFIC THERAPIES AND OTHER EXPLORATORY STUDIES

A small number of other therapies have been discussed and have limited clinical study data. These include a recombinant vaccine using *Escherichia coli*–encapsulated peanut proteins[61]; a Chinese herbal formulation, Food Allergy Herbal Formula 1[62]; mature retinoic acid–differentiated dendritic cell LAG3 regulatory T cells[63]; and peanut peptides.[60] Each of these approaches are in various stages of development but none have progressed to the stage of large scale clinical trials. The effect of the microbiome in response to these and other therapies is largely unknown, but it will be fascinating to learn more about this in the coming years.[64]

CONCLUSION

In comparing the different types of immunotherapy for food allergy, OIT has the greatest amount of clinical desensitization, followed by SLIT and then EPIT, whereas allergic side effects to the treatments are in the same order, with OIT having the most.[18,36,57] As noted above, a significant number of clinical trials for immunotherapy have been conducted, but continued knowledge gaps exist about their use.[65-68] In particular, the current body of scientific investigation is limited by the small study population of most clinical trials to date, the variability of clinical trial designs, the diversity of outcomes tested, the paucity of available immunologic biomarkers correlating with clinical outcomes, the lack of economic impact data,[69] and the relative lack of diversity in study populations (both in age distribution and race/ethnicity composition, Table VI). Studies have also been limited in scope, with few studies evaluating potential long-term safety issues. Additionally, data are limited to a few studies in subjects with peanut, egg, and milk allergy that attempt to address our knowledge gap in long-term clinical outcomes and key questions, such as the ability to maintain a state of SU after successful allergen immunotherapy versus the potential for relapse into a fully allergic state.[12,17] If these products are approved by regulators, then their use in clinical management remains to be determined; the balance between avoidance without ongoing symptoms but fear of an accidental allergic reaction and treatment possibly providing some protection from accidental ingestion but with ongoing side effects will be decided on a single-patient basis (Table VI).[70,71]

What do we know?

- **Food immunotherapy causes desensitization in most patients.**
- **OIT has shown the greatest promise for efficacy in terms of the amount of protein that can be ingested and has also demonstrated less tolerability and a less favorable safety profile.**
- **SLIT and EPIT, which offer the least desensitization, have the best safety and tolerability profiles.**
- **Studies have been conducted with adding adjuvants and anti-IgE to either enhance the efficacy or safety of food immunotherapy.**

What is still unknown?

- **The optimal dose, frequency, and duration of OIT are unknown.**
- **Is maintenance therapy or food ingestion required to maintain SU (clinical remission)? If so, at what dose and what frequency?**
- **Will any type of food immunotherapy compared with conventional treatment change quality of life in children with food allergy?**
- **Is a combination or sequence of either OIT, SLIT, or EPIT better than one treatment alone?**

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