REVIEW

The clinical and immune outcomes after food allergen immunotherapy emphasizing the development of tolerance

Jennifer M. Miller[a,b], *Carla M. Davis*[a,b], *and Sara Anvari*[a,b]

Purpose of review
The present review serves to outline the direction of food allergy immunotherapy research with an emphasis on clinical and immunologic outcomes. It helps to delineate sustained unresponsiveness achieved from food immunotherapy as the clinical outcome most similar to immune tolerance.

Recent findings
We will discuss the difference between immune tolerance, desensitization, and sustained unresponsiveness in relation to food immunotherapy by discussing the clinical and immunologic changes which have been recently discovered.

Summary
Research has recently shown that oral immunotherapy is most efficacious clinically at achieving desensitization to a food and sustained unresponsiveness.

Keywords
desensitization, food allergy, food immunotherapy, sustained unresponsiveness

INTRODUCTION

Between 1997 and 2011, the Centers for Disease Control and Prevention reported an increased prevalence of food allergies from 3.4 to 5.1% [1]. Recent studies have reported a further increase in food allergy prevalence, with 8% in children and 11% in adults [2▪,3▪]. The rising prevalence has led to the investigation of potential treatment options. At this time, standard of care for food allergies is strict food allergen avoidance and immediate treatment of anaphylactic reactions with intramuscular epinephrine [4,5]. Currently, there are no Food and Drug Administration (FDA) approved treatments for food allergies; however, significant advances in food immunotherapy research have been made in the field of oral, sublingual, and epicutaneous immunotherapy [5,6▪,7,8].

At the basis of immunotherapy are the concepts of immune tolerance, desensitization, and sustained unresponsiveness. Immune tolerance, seen in non-food allergic individuals, is the absence of immune reactivity to a food antigen, and the ability to consume food ad lib without clinical symptoms. Desensitization is the primary goal of immunotherapy in patients lacking immune tolerance to a food. Food desensitization is a temporary state of antigen hyporesponsiveness, achieved and maintained by daily administration of the food. Interruption of dosing can lead to a loss of this desensitization. The second goal of immunotherapy is sustained unresponsiveness, which is similar to tolerance, except that it is achieved in food allergic individuals who have been successfully desensitized following food immunotherapy. To assess sustained unresponsiveness, an individual undergoing food immunotherapy must be able to stop therapy for a minimum 1–2 months and ingest the food allergen without clinical reactivity [9▪▪].

Clinical trial outcomes for oral, sublingual, and epicutaneous immunotherapy for various food

[a]Department of Pediatrics, Section of Immunology, Allergy and Retrovirology, Baylor College of Medicine and [b]Department of Pediatrics, Section of Immunology, Allergy and Retrovirology, Texas Children's Hospital, Houston, Texas, USA

Correspondence to Sara Anvari, MD, MS, 1102 Bates Avenue, MC Suite 330.01, Houston, Texas 77030, USA. Tel: +1 832 824 1319; fax: +1 832 825 1260; e-mail: Sara.Anvari@bcm.edu

Curr Opin Pediatr 2019, 31:821–827

DOI:10.1097/MOP.0000000000000831

1040-8703 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

KEY POINTS

- Food allergen immunotherapy is an upcoming treatment for food allergy, which encourages an immunologic change to allow the development of desensitization and sustained unresponsiveness to previously allergenic food protein.
- The basic mechanism of action of immunotherapy is that dendritic cells in the gut, mucosa, or skin take up the food allergen and present them in the lymphatic system where there is contraction of the allergen specific T cells and effector cells and expansion of the tolerogenic T cells, B cells, and effector cells.
- Of the types of immunotherapy, OIT appears to have the most convincing research showing its efficacy in desensitizing a patient and building sustained unresponsiveness. However, it also has a larger side-effect profile compared to EPIT and SLIT. EPIT and SLIT have a smaller side effect profile, but the recent studies indicate less efficacy compared to OIT.

antigens have been published and have reported the overall outcomes of desensitization for the different forms of treatment (Table 1). So far, it has been shown that desensitization can be achieved with immunotherapy; however, sustained unresponsiveness is still a challenge and has been reported from 27 to 50% in children and adults and up to 78% in the preschool age group [10▪▪]. At this time, immunotherapy for food allergies are still under evaluation by the FDA, but they may be approved in the near future. It is important to understand the underlying immune modulations associated with these treatments that help promote desensitization. This review will discuss how different forms of immunotherapy achieve desensitization and sustained unresponsiveness, and the clinical and immunologic outcomes.

MECHANISM OF ACTION

The immune system is continuously exposed to various antigens and depending on the presentation, it determines whether the antigen is either innocuous or harmful. In patients exhibiting food tolerance, the immune system recognizes the food as nonthreatening. However, in food allergic patients, the immune system has a heightened response to the unique peptides that make up the food protein which subsequently leads to an allergic response, such as anaphylaxis. The mechanism of immunotherapy is to desensitize the immune system's hyperresponsiveness to an antigen and allow for allergen exposure without clinical reactivity. The immunomodulatory mechanisms behind immunotherapy differ depending on the form of immunotherapy.

In oral immunotherapy (OIT), the ingested allergen is taken up by gastrointestinal dendritic cells in the lamina propria of the small intestines [11]. The dendritic cells process the antigen and transfer to lymphoid tissue, where they present the antigen to $CD4^+$ T cells in the mesenteric lymph nodes. The T-cell response includes initial expansion of the allergen-specific T helper 2 cells and effector cells, such as basophils, mast cells, and eosinophils early in OIT. However, later during OIT buildup, contraction of the T helper 2 cells leading to suppression of the effector cells, their cytokines and B cells producing allergen-specific immunoglobulin E (IgE). Additionally, there is upregulation of allergen-specific immunoglobulin G4 (IgG4) from B cells and hypomethylation of the transcription factor forkhead box protein 3 (FOXP3) thus leading to an expansion of antigen specific T regulatory cells, thus promoting successful desensitization and potentially sustained unresponsiveness [11–16]. Adjuvants used during OIT, such as anti-IgE (omalizumab) or probiotics have also demonstrated increased efficacy and safety of OIT through specific and nonspecific

Table 1. Immunotherapy methods for food allergies

Immunotherapy characteristics	Oral immunotherapy	Sublingual immunotherapy	Epicutaneous immunotherapy
Daily food protein Doses	300–4000 mg	2–7 mg	50–500 mcg
Foods studied	Cow's milk, egg, peanut, walnut, cashew, wheat	Cow's milk, peanut, hazelnut, peach	Cow's milk, peanut
Route of delivery	Powder	Liquid drops	Patch
Common side effects	Oral or gastrointestinal most common; systemic reactions possible including anapylaxis	Oral or local pharyngeal effects	Local skin
Clinical Desensitization	70–90% [9▪▪,22▪,27,28,47▪▪,48]	10–70% [42,44]	14–60%, depending on age [38▪▪,39,49]
Sustained Unresponsiveness	27–78%, dependent on age [10▪▪]	~10% [46,51]	Unknown

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

modulation of immune effector components. unresponsiveness [17,18,19▪,20▪,21,22▪].

As for sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT), the allergen is taken up by Langerhans cells in the oral mucosa and epidermis, respectively. The Langerhans cells from the oral mucosa stimulated by SLIT present antigen to T cells in the submandibular lymph nodes, and the Langerhans cells from the epidermis stimulated by EPIT present antigen to T cells in the regional lymph nodes, which lead to similar changes in allergen specific, T helper 2, effector cells, allergic specific IgE, and IgG4 responses.

BASICS OF ORAL IMMUNOTHERAPY

Of the different forms of food immunotherapy, oral immunotherapy (OIT) has been the most extensively researched. OIT has been studied with peanut, cashew, walnut, cow's milk, egg, and wheat. OIT protocols start with the daily ingestion of a small amount of food protein and doses are increased every 2–4 weeks until a target dose is achieved. This is known as the OIT 'build-up phase', which lasts approximately 6–12 months. The majority of patients react during the build-up phase and may experience mild oropharyngeal itching, urticaria, abdominal pain, and/or nausea. The prevalence of eosinophilic esophagitis associated with OIT is 2.7% [23]. Risk of anaphylaxis can be increased when doses are taken on an empty stomach, during illness and/or fever, during menstruation, or right before exercise. The target dose of OIT ranges from minimum of 300 mg, which is the equivalent of two to three small peanuts and the threshold of cross-contamination, to a maximum of 4000 mg. The patient remains on this daily 'maintenance dose' for months to years. To assess sustained unresponsiveness following OIT, the patient undergoes a 'wash-out period' by discontinuing treatment for a few weeks or months prior to a food challenge. This food challenge assesses whether a desensitized patient can achieve sustained unresponsiveness, which includes clinical tolerance without continued daily allergen dosing. The safety profile for OIT is less desirable when compared to other forms of immunotherapy. The efficacy of OIT is favorable with 70–90% of patients achieving desensitization; however, sustained unresponsiveness is typically less than 50% of subjects but higher in the preschool age group [14,24–28,29▪,30–32,33▪,34,35▪,36▪].

BASICS OF EPICUTANEOUS IMMUNOTHERAPY

Epicutaneous immunotherapy (EPIT) utilizes a novel antigen delivery method through the skin as a way to increase an individual's threshold of reactivity to a food allergen. In EPIT, the allergen binds to an adhesive patch via electrostatic force. The patch is placed on the interscapular area or the back of the arm. Condensation from the patient's sweat releases the allergen from the patch to the surface of the skin [37–39]. The daily maintenance dose studied in EPIT has ranged from 50 to 500 μg, with the maintenance dose of 250 μg selected because of optimal efficacy and lowest adverse events. EPIT has been studied for IgE-mediated peanut and cow's milk allergy and eosinophilic esophagitis. In recent peanut EPIT trials, patients typically received 250 μg of the peanut protein adhered to the patch and underwent a build-up and maintenance phase. During the build-up phase, the patch was worn for 3 h on Day 1 under medical supervision, followed by 6 h per day during the first week, 12 h per day during the second week, and then 24 h per day, with a new patch applied in a different location of the interscapular region or back of the arm, thus beginning the maintenance period. Overall, the safety profile of EPIT is considered favorable compared to OIT, with most patients experiencing only local skin reactions. Activity is not restricted with EPIT. The efficacy of EPIT, however is more modest compared to OIT. Sustained unresponsiveness has not been assessed in patients undergoing EPIT trials [37–40].

BASICS OF SUBLINGUAL IMMUNOTHERAPY

Sublingual immunotherapy (SLIT) entails a patient placing a liquid extract of food protein sublingually for a few minutes and then swallowing it. Depending on the antigen, the starting doses ranged from 2×10^{-11} to 1.65×10^{-7} dose is started in the range of micrograms and then gradually increased every 2 weeks in an escalation phase and maintained at a daily dose [9▪▪,41–42]. The maintenance dose is considerably smaller than OIT doses ranging from 2 to 7 mg/day of food protein [34,43–44]. SLIT has been studied in peanut, cow's milk, hazelnut, and peach allergic patients. The safety profile of SLIT is much more favorable than OIT, with primarily transient oropharyngeal symptoms reported in more than 95% of subjects. Patients taking SLIT treatment are advised to avoid eating for 30 min after dose administration. Overall, SLIT studies have demonstrated less desirable efficacy [41,44,45▪].

CLINICAL OUTCOMES OF ORAL IMMUNOTHERAPY

When comparing the clinical outcomes for the different forms of immunotherapy, OIT is superior

1040-8703 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

to SLIT and EPIT, with 70–90% of patients achieving desensitization, compared to 10–70% and 35%% in SLIT and EPIT patients, respectively [38▪▪,44,46]. A recently published phase III peanut OIT trial demonstrated safety and efficacy of peanut OIT in peanut allergic children and adults. The study included 551 patients reacting to 100 mg or least with initial peanut double-blind, placebo-controlled food challenge (DBPCFC). Subjects were randomized to peanut OIT or placebo at a maintenance dose of 300 mg daily for 24 weeks and then underwent a DBPCFC to assess desensitization. Responders were defined as patients tolerating at least 600 mg of a peanut challenge dose without symptoms. When comparing treated pediatric patients (4–17 years) with placebo patients, the study demonstrated good efficacy with 63.2% more patients on treatment tolerating a dose at least 600 mg of peanut protein without dose-limiting symptoms and lower symptom severity during the exit food challenge than placebo. Efficacy was not significant in the group more than 18 years of age. Adverse events occurred in the majority of subjects during the intervention period, with most being mild to moderate [47▪▪].

Desensitization by OIT has been promising with good efficacy, however sustained unresponsiveness has been variable, ranging from 27 to 78% depending on the food, duration off treatment and age. A pilot study assessing sustained unresponsiveness in 39 patients between 1 and 16 years of age treated for 5 years with peanut OIT demonstrated outcomes in 24. Twelve of 24 successfully passed a DBPCFC one month after stopping OIT and were labeled as sustained nonresponders. It was noted that patients who achieved sustained unresponsiveness had smaller skin test wheal sizes [48]. In 2017, Vickery *et al.* enrolled 40 peanut allergic children between 9 and 36 months and treated with daily maintenance doses of 300 mg ($n = 20$) or 3000 mg ($n = 20$) for 3 years, followed by a 1-month avoidance period and a food challenge. Thirty-seven (81%) patients achieved successful desensitization (low-dose = 17/20; high-dose = 13/17). Sustained unresponsiveness after 4 weeks of peanut avoidance was achieved in 71% of the high-dose group and 85% in the low-dose group [10▪▪].

OIT studies have also assessed efficacy of treatment and speed at which maintenance is achieved when using the adjuvant omalizumab (monoclonal anti-IgE) prior to initiating single or multifood OIT in food allergic subjects [19▪,20▪,21,22▪]. In the study by MacGinnitie *et al.*, 79% of subjects receiving omalizumab for 12 weeks successfully achieved rapid peanut OIT desensitization (2 g of peanut protein) 6 weeks after stopping omalizumab compared to 12.5% of peanut OIT treatment with placebo drug. The study demonstrated that omalizumab-treated patients could achieve the maintenance dose faster compared to those without treatment [22▪].

CLINICAL OUTCOMES OF EPICUTANEOUS IMMUNOTHERAPY

In 2017, the phase II peanut EPIT study compared patients between the ages of 6–49 years on 100 μg EPIT ($n = 24$) versus 250 μg EPIT ($n = 25$) versus placebo ($n = 25$). Desensitization (defined by passing a 5044 mg protein challenge or achieving a 10-fold increase in consumed dose from baseline) was achieved in 46% receiving 100 μg, 48% receiving 250 μg, and 12% in the placebo group. Treatment success was higher in the 4- to 11-year old (61%) compared to those more than 11 years old (14.4%) [39]. A subsequent phase IIb peanut EPIT study evaluating a 12-month treatment with 50, 100, 250 μg peanut EPIT versus placebo was performed in patients 6–55 years of age. The study showed a significant absolute response rate difference of 25% between the 250 μg patch versus placebo. When stratifying by age, the response rate difference between 250 μg versus placebo was most significant in the 6- to 11-year old (34.2%) with no significant difference among adolescents/adults (14.4%). This study suggested use of the higher dose patch in the younger age group [49]. The recently published phase III peanut EPIT assessed the efficacy of the 250 μg patch in patients between 4 and 11 years of age. A statistically significant difference in responder rate was observed between patients receiving 12 months of 250 μg peanut EPIT versus placebo (difference 21.7%; CI, 12.4–29.8%; $P < 0.001$) [38▪▪].

CLINICAL OUTCOMES OF SUBLINGUAL IMMUNOTHERAPY

In 2011, a double-blind placebo controlled study evaluating the efficacy of peanut SLIT was performed in 18 patients ages 1–11 years. Patients underwent a 6-month escalation period receiving either active treatment ($n = 11$) or placebo ($n = 7$) followed by 6 months of maintenance (2 mg protein). Patients who received active treatment tolerated 20 times more peanut protein compared to patients receiving placebo, with a median tolerated dose of 1710 mg in the treatment group versus 85 mg in the placebo group ($P = 0.011$) [50].

In 2013, a peanut SLIT study noted a modest increase in desensitization in 12- to 37-year old after 44 weeks of peanut SLIT (maintenance 1386 μg) in up to 70% ($n = 14/20$) of subjects on SLIT compared to 15% ($n = 3/20$) of subjects on placebo [42]. A follow-up open-label study evaluated response rates

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

in the same group of patients after 2 and 3 years of peanut SLIT and assessing sustained unresponsiveness after 8 weeks of treatment cessation. The study concluded a large drop-out rate (>50%), only 10.8% of subjects ($n=4$) were fully desensitized (5 g protein) after 3 years, and all four subjects achieved sustained unresponsiveness [44].

A comparison study between peanut SLIT and OIT revealed that desensitization was achieved after 12-month of maintenance with both treatments, however the median challenge threshold dose was significantly greater with OIT (141-fold increase) than with SLIT (22-fold increase). In addition, following 4 weeks of treatment cessation, sustained unresponsiveness was achieved in only 10% of patients undergoing SLIT versus 27% undergoing OIT [51].

IMMUNOLOGICAL OUTCOMES OF ORAL IMMUNOTHERAPY

The immunodulatory effects of OIT have yet to be fully elucidated. Studies have demonstrated that the development of desensitization has been established through immune modulatory effects on effector cells, such as mast cells and basophils, $CD4^+$ T cells, antigen-specific B cells and allergen specific IgE, IgG4, and IgA. During the initial period of OIT, repeated exposure to low doses of food allergen causes hyporesposiveness of the effector cells leading to a reduction of the high-affinity IgE receptors and eventually leading to the reduction of allergen specific IgE levels. This in turn explains the reduced skin prick test wheal size and basophil activation in response to the antigen during OIT [12▪,52,53▪,54]. The Th2 pathway is upregulated in patients with food allergies and is sustained by epithelial derived mediators such as thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25) and IL-33 [55]. In the early phases of OIT, low doses of antigen continue to promote Th2 cell stimulation of B cells via cytokines such as IL-4, IL-5, and IL-9 to further expand antigen specific IgE, which explains the initial rise of IgE during the first few months of OIT. As OIT progresses and antigen doses increase to the maintenance dose, an increase in IL-10-producing $CD4^+$ T cells occurs and induces the production of allergen-specific T-regulatory cells. Additionally, hyporesponsiveness of effector cells, and an increase in antigen specific IgG4, IgA and a decrease in antigen specific IgE levels produced by B cells is seen during this period [12▪]. When comparing OIT with SLIT, a significantly larger increase in peanut specific IgG4 was observed at all time points in OIT and peanut specific IgE was similar until 6 months when there was a significant reduction in those receiving OIT.

In patients who achieved sustained unresponsiveness, it was observed that they had lower peanut specific IgE levels, including Ara h1 and Ara h2 specific IgE, when compared to the patients who did not reach sustained unresponsiveness. No difference in peanut specific IgG4 was observed between patients achieving sustained unresponsiveness and those who did not [10▪▪,48].

IMMUNOLOGICAL OUTCOMES OF EPICUTANEOUS IMMUNOTHERAPY

In EPIT, it is believed that the immunomodulatory effects of the treatment leading to the downregulation of the effector cell responses are regulated by the activation of epidermal Langerhans cells via antigen contact through the skin. The Langerhans cells from the epidermis stimulated by EPIT present antigen to T cells in the regional lymph nodes, thus producing the immune changes in T effector, T helper 2, IgE, and IgG4 responses. Additionally, gut-homing Tregs ($LAP1^+FOXP3^+$) are believed to provide the protection that develops from treatment [39]. A recently published study on peanut EPIT in children demonstrated an improvement in peanut-specific IgE levels at month 3 and 6, however the levels returned to baseline by month 12. In contrast, peanut-specific IgG4 increased over time [38▪▪]. Basophil activation and peanut-specific Th2 cytokines were also observed to be reduced with peanut EPIT [39].

IMMUNOLOGICAL OUTCOMES OF SUBLINGUAL IMMUNOTHERAPY

The immunomodulatory effects of SLIT treatment are mediated by the uptake of antigen by oral mucosal Langerhans cells, stimulated by SLIT to present antigen to T cells in the submandibular lymph nodes, leading to changes in T effector, T helper 2, IgE, and IgG4 responses [56–57]. A previous study evaluating 1–11 year-old peanut allergic subjects who underwent peanut SLIT for 1 year demonstrated peanut-specific IgE levels increase in the first 4 months ($P=0.002$) and then decrease over the remaining 8 months ($P=0.003$). Furthermore, the peanut-specific IgG4 increased over 12 months ($P=0.014$). Statistically significant changes were not observed in the levels of IL-13, IL-10, IFN-γ, or T-regulatory cells [50]. There was not a statistically significant difference between peanut specific IgE or IgG4 in patients who did and did not achieve sustained unresponsiveness [44].

The immunological changes for each immunotherapy delivery type which are described above are summarized in Table 2.

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Table 2. Immunological changes for each immunotherapy method

Immunotherapy route	Initial phase cells and cytokines	Late phase cells and cytokines	Immunoglobulin changes	Sustained unresponsiveness (SU)
Oral Immunotherapy	Promote Th2 cell stimulation of B cells via IL-4, IL-5, IL-9 [12▪,55]	Increase in IL-10 producing $CD4^+$ T cells Increase in allergen-specific T-regulatory cells [12▪]	Initial increase in antigen-specific IgE then decrease Increase in antigen-specific IgG4 and IgA [12▪,52,53▪,54]	Lower-specific IgE levels and similar antigen-specific IgG4 in patients with SU [10▪▪,48]
Sublingual Immunotherapy	Regulated by oral mucosal Langerhans cells and then T effector and T helper 2 cells [56,57]	No statistically significant change in IL-10, IL-13, IFN-γ, or T-regulatory cells [50]	Increase in allergen-specific IgE for first 4 months and then decrease Increase in allergen-specific IgG4 from beginning [50]	Not a statistically significant difference in antigen-specific IgE or IgG4 between those who did or did not reach SU [44]
Epicutaneous immunotherapy	Regulated by epidermal Langerhans cells and gut-homing Tregs [44]	Decrease in basophil activation and peanut-specific Th2 cytokines [44]	Decrease in antigen-specific IgE at month 3 and 6 and return to baseline at month 12, increase in antigen-specific IgG4 over time [38▪▪]	Unknown

CONCLUSION

With the rising prevalence of food allergies, well tolerated and effective therapies are needed. Immune tolerance is the body's natural state of enabling a food to be consumed without reaction. If a patient reaches this state following immunotherapy it is considered sustained unresponsiveness. The most recent literature shows good efficacy of desensitization via oral immunotherapy indicated by successful food challenges and immunologic changes. However, this desensitization requires continued daily dosing of the food allergen. The success rate of sustained unresponsiveness is still being evaluated and may only be successful in up to 50% most cases, excluding preschool aged patients. Clinical desensitization by SLIT and EPIT have been shown to have modest efficacy. More studies in SLIT and EPIT needed to further assess desensitization in younger patients.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

C.M.D. and S.A. receive grant support from Regeneron, Aimmune Therapeutics, and DBV Technologies. J.M. has no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:
▪ of special interest
▪▪ of outstanding interest

1. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States, 1997-2011. NCHS Data Brief 2013; (121):1–8.
2. ▪ Gupta RS, Warren CM, Smith BM, *et al.* The public health impact of parent-reported childhood food allergies in the United States. Pediatrics 2018; 142:1–12.

The overall prevalence of food allergy in children has increased to approximately 8%.

3. ▪ Gupta RS, Warren CM, Smith BM, *et al.* Prevalence and severity of food allergies among US adults. JAMA Network Open 2019; (2):1–14.

The overall prevalence of food allergy in adults has increased to approximately 11%.

4. Boyce JA, Assa'ad A, Burks AW, *et al.* Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. J Allergy Clin Immunol 2010; 126:1105–1118.
5. Sampson HA, Aceves S, Bock SA, *et al.* Food allergy: a practice parameter update. J Allergy Clin Immunol 2014; 134:1016–1025.
6. ▪ du Toit G, Sampson HA, Plaut M, *et al.* Food allergy: update on prevention and tolerance. J Allergy Clin Immunol 2018; 141:30–40.

Use of food allergy immunotherapy decreases the response of the immune system to the allergen.

7. Pajno GB, Fernandez-Rivas M, Arasi S, *et al.* EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. Allergy 2018; 73: 799–815.
8. Nurmatov U, Dhami S, Arasi S, *et al.* Allergen immunotherapy for IgE-mediated food allergy: a systematic review and meta-analysis. Allergy 2017; 72:1133–1147.
9. ▪▪ Gernez Y, Nowak-Wegrzyn A. Immunotherapy for food allergy: are we there yet? J Allergy Clin Immunol Pract 2017; 5:250–272.

Extensive review of previous food allergen immunotherapy trials

10. ▪▪ Vickery BP, Berglund JP, Burk CM, *et al.* Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol 2017; 139:173–181.

This literature showed the high levels of sustained unresponsiveness in some peanut OIT patients.

11. Vickery BP, Scurlock AM, Jones SM, Burks AW. Mechanisms of immune tolerance relevant to food allergy. J Allergy Clin Immunol 2011; 127: 576–584.

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

12. Kulis MD, Patil SU, Wambre E, Vickery BP. Immune mechanisms of oral
■ immunotherapy. J Allergy Clin Immunol 2018; 141:491–498.
Typically with oral immunotherapy there is a suppression of the specific allergen IgE and an increase in the specific allergen IgG4.

13. Wang M, Yang IV, Davidson EJ, *et al.* Forkhead box protein 3 demethylation is associated with tolerance induction in peanut-induced intestinal allergy. J Allergy Clin Immunol 2018; 141:659–670.

14. Jones SM, Burks AW, Dupont C. State of the art on food allergy immunotherapy: oral, sublingual, and epicutaneous. J Allergy Clin Immunol 2014; 133:318–323.

15. Sampson HA, O'Mahony L, Burks AW, *et al.* Mechanisms of food allergy. J Allergy Clin Immunol 2018; 141:11–19.

16. Kiyotani K, Mai TH, Yamaguchi R. Characterization of the B-cell receptor repertoires in peanut allergic subjects undergoing oral immunotherapy. J Hum Genet 2018; 63:239–248.

17. Tang ML, Ponsonby AL, Orsini F, *et al.* Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol 2015; 135:737–744.

18. Hsiao KC, Ponsonby AL, Axelrad C, *et al.* Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4-year follow-up of a randomized, double-blind, placebo-controlled trial. Lancet Child Adolesc Health 2017; 1:97–105.

19. Andorf S, Purington N, Block WM, *et al.* Anti-IgE treatment with oral im-
■ munotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. Lancet Gastroenterol Hepatol 2018; 3:85–94.
The use of omalizumab may help improve the overall effect of oral immunotherapy and may decrease the risk of adverse effects

20. Fischmeyer-Guerrerio PA, MAsilamani M, Gu W, *et al.* Mechanistic correlates
■ of clinical responses to omalizumab in the setting of oral immunotherapy for milk allergy. J Allergy Clin Immunol ; 140:1043–1053.e8.
The use of omalizumab with milk OIT may be more helpful in a specific subset of patients based on baseline biomarkers.

21. Brandstrom J, Vetander M, Lilja G, *et al.* Individually dosed omalizumab: an effective treatment for severe peanut allergy. Clin Exp Allergy 2017; 47:540–550.

22. MacGinnitie AJ, Rachid R, Gragg H, *et al.* Omalizumab facilitates rapid oral
■ desensitization for peanut allergy. J Allergy Clin Immunol 2017; 139:873–881.
Omalizumab can be used to speed up the build-up phase and possibly increase the dose a patient can consume without symptoms.

23. Lucendo AJ, Arias A, Tenias JM. Relation between eosinophilic esophagitis and oral immunotherapy for food allergy: a systematic review with meta-analysis. Ann Allergy Asthma Immunol 2014; 113:624–629.

24. Blumchen K, Ulbricht H, Staden U, *et al.* Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol 2010; 126:83–91.

25. Varshney P, Jones SM, Scurlock AM, *et al.* A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol 2011; 127:654–660.

26. Anagnostou K, Islam S, King Y, *et al.* Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet 2014; 383:1297–1304.

27. Bird JA, Feldman M, Arneson A, *et al.* Modified peanut oral immunotherapy protocol safely and effectively induces desensitization. J Allergy Clin Immunol Pract 2015; 3:433–435.

28. Kivisto JE, Korppi M, Helminen M, *et al.* Half of the children who received oral immunotherapy for a cows' milk allergy consumed milk freely after 2.5 years. Acta Paediatr 2015; 104:1164–1168.

29. Nagakura KL, Sato S, Yanagida N, *et al.* Oral immunotherapy in japanese
■ children with anaphylactic peanut allergy. Int Arch Allergy Immunol 2018; 175:181–188.
The use of OIT can be used to achieve sustained unresponsiveness in patients with previously history of anaphylaxis. 100% of 22 patients achieved desensitization, 68.1% of these had SU after 2 years compared to 2/11 in the control group.

30. Akashi M, Yasudo H, Narita M, *et al.* Randomized controlled trial of oral immunotherapy for egg allergy in Japanese patients. Pediatr Int 2017; 59:534–539.

31. Freeland DMH, Manohar M, Andorf S, *et al.* Oral immunotherapy for food allergy. Semin Immunol 2017; 30:36–44.

32. Wasserman RL, Jones DH, Windom HH. Oral immunotherapy for food allergy: the FAST perspective. Ann Allergy Asthma Immunol 2018; 121:272–275.

33. Wood RA. Oral immunotherapy for food allergy. J Investig Allergol Clin
■ Immunol 2017; 27:151–159.
Good discussion of oral immunotherapy for food allergen.

34. Scurlock AM. Oral and sublingual immunotherapy for treatment of IgE-mediated food allergy. Clin Rev Allergy Immunol 2018; 55:139–152.

35. Anvari S, Anagnostou K. The nuts and bolts of food immunotherapy: the future
■ of food allergy. Children (Basel) 2018; 5:pii: E47.
Synopsis of food immunotherapy at the understanding of a general pediatrician.

36. Rekabi M, Arshi S, Bemanian MH, *et al.* Evaluation of a new protocol for wheat
■ desensitization in patients with wheat-induced anaphylaxis. Immunotherapy 2017; 9:637–645.
Use of OIT for wheat is efficacious and safe requiring more research.

37. Langlois A, Graham F, Begin P. Epicutaneous peanut patch device for the treatment of peanut allergy. Exp Rev Clin Immunol 2019; 15:449–460.

38. Fleischer DM, Greenhawt M, Sussman G, *et al.* Effect of epicutaneous
■■ immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES Randomized Clinical Trial. JAMA 2019; 321:946–955.
The most recently published study discussing the efficacy and immunologic changes with the use of EPIT for peanut allergy. It showed statistical significance but not clinical significance in patients with EPIT.

39. Jones SM, Sicherer SH, Burks AW, *et al.* Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol 2017; 139:1242–1252.

40. Dupont C, Kalach N, Soulaines P, *et al.* Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol 2010; 125:1165–1167.

41. Enrique E, Pineda F, Malek T, *et al.* Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract 2. J Allergy Clin Immunol 2005; 116:1073–1079.

42. Fleischer DM, Burks AW, Vickery BP, *et al.* Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol 2013; 131:119–127.

43. Akdis CA, Barlan IB, Bahceciler N, Akdis M. Immunological mechanisms of sublingual immunotherapy. Allergy 2006; 61(Suppl 81):11–14.

44. Burks AW, Wood RA, Jones SM, *et al.* Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol 2015; 135:1240.e3–1248.e3.

45. Gomez F, Gogas G, Gonzalez M, *et al.* The clinical and immunologic effects of
■ Pru p 3 sublingual immunotherapy on peach and peanut allergy in patients with systemic reactions. Clin Exp Allergy 2017; 47:339–350.
Use of Pru P 3 SLIT lead to desensitization in peach allergic patients and may affect peanut allergic patients.

46. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, *et al.* The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 2012; 129:448–455.

47. The PALISADE Group of Clinical Investigators. AR101 oral immunotherapy
■■ for peanut allergy. NEJM 2018; 379:1991–2001.
This studied the use of peanut OIT and showed a significant improvement in desensitization for children but not adults.

48. Vickery BP, Scurlock AM, Kulis M, *et al.* Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol 2014; 133:468–475.

49. Sampson HA, Shreffler WG, Yang WH, *et al.* Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. JAMA 2017; 318:1798–1809.

50. Kim EH, Bird JA, Kulis M, *et al.* Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol 2011; 127:640–646.

51. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, *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; 135:1275–1282.

52. Perez-Rangel I, Rodriquez DR, Escudero C, *et al.* Efficacy and safety of high-dose rush oral immunotherapy in persistent egg allergic children: A randomized clinical trial. Ann Allergy Asthma Immunol 2017; 118:356–364.e3.

53. Uotila R, Kukkonen AK, Greco D, *et al.* Peanut oral immunotherapy decreases
■ IgE to Ara h 2 and Ara h 6 but does not enhance sensitization to cross-reactive allergens. J Allergy Clin Immunol 2017; 139:1393–1396.e6.
Discusses the decrease in peanut specific IgE in a studied group following OIT.

54. Tao B, Morris S, Grzeskowiak L, *et al.* Sequential hypoallergenic boiled peanut and roasted peanut oral immunotherapy. Error! Hyperlink reference not valid 2017; 47:1501–1504.

55. Han H, Roan F, Ziegler SF. The atopic march: current insights into skin barrier dysfunction and epithelial cell-derived cytokines. Immunol Rev 2017; 278:116–130.

56. Tanaka Y, Fukumoto S, Sugawara S. Mechanisms underlying the induction of regulatory T cells by sublingual immunotherapy. J Oral Biosci 2019; 61:73–77.

57. Palomares F, Gomez F, Bogas C, *et al.* Immunological changes induced in peach allergy patients with systemic reactions by Pru p 3 sublingual immunotherapy. Mol Nutr Food Res 2018; 62:. doi: 10.1002/mnfr.201700669.

1040-8703 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.