Food allergy: History, definitions and treatment approaches

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ABSTRACT

Allergen-specific immunotherapy for the treatment of immunoglobulin E mediated food allergies, specifically oral, epicutaneous, and sublingual immunotherapies, are promising options that may provide an alternative to strict avoidance of the dietary allergen. Of these potential therapies, oral immunotherapy is the furthest along in development, with strong evidence of efficacy in clinical trials, and has achieved regulatory approval. Nevertheless, oral immunotherapy may not be a suitable therapy for some patients due to the risk of adverse effects. In contrast to oral immunotherapy, epicutaneous and sublingual immunotherapies have demonstrated modest efficacy in clinical trials, with a favorable adverse effect profile, which suggests that these therapies may be possible contenders to oral immunotherapy in certain clinical situations. Familiarity with the various treatment approaches is vital for guiding patients and families as more therapeutic modalities become available for use outside of the research setting.

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For generations, the mainstay for food allergy treatment has been strict avoidance of the dietary allergen; however, this approach is not without inadequacies, as evident by the constant vigilance required on the part of patients and families to avoid accidental exposures, and the fear of reacting to allergen-contaminated foods. The considerable distress caused by the burden of food allergy and the negative impact on quality of life highlights the urgent need for alternative strategies. Subcutaneous immunotherapy, also referred to as "allergy shots," is a well-studied modality for the management of allergic rhinitis and venom hypersensitivity.

In a similar fashion, subcutaneous immunotherapy was attempted for peanut allergy in the early 1990s; however, this endeavor was halted due to safety concerns.[1] Other food immunotherapy approaches, such as oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT), have been shown to be promising tools for food allergy treatment, with the primary intent of modifying the immune response to a food allergen to achieve desensitization and, ideally, tolerance to an allergenic food. Of these treatments, OIT is the most vetted, with considerable evidence in clinical trials and is the only modality with a regulatory approved product for peanut allergy. Here, we reviewed the most common food allergy immunotherapy approaches (OIT, SLIT, and EPIT) and discuss the strengths, limitations, and stage in development for each therapeutic modality.

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OIT HISTORY

In 1908, the first successful case of OIT for food allergy was published in *The Lancet* by Schofield,[2] who desensitized a 13-year-old boy with egg allergy. Beginning in the 1980s, Patriarca *et al*.,[3] in Europe, published some of the earliest OIT protocols for the treatment of cow's milk, egg, and fish allergies. Although these early studies showed promising results, literature on OIT remained sparse until the beginning of the 21st century. In the early 2000s, additional studies by Patriarca *et al*.[4] and Meglio *et al*.[5] described protocols that started with a single dose of the allergen on the first day, followed by dose increases at varying intervals (*e.g.*, daily, weekly, or every 2 weeks) until reaching maintenance. However, some participants were unable to achieve maintenance when using this protocol.[4,5]

In 2007, Buchanan *et al*.[6] published the first proof-of-concept study, which established the safety of OIT in a small cohort of patients with nonanaphylactic egg allergy. It was postulated that the inability of some participants to achieve maintenance in previous studies was due to inadequate initial desensitization. Therefore, this study incorporated an initial "modified rush phase" on the first day of the

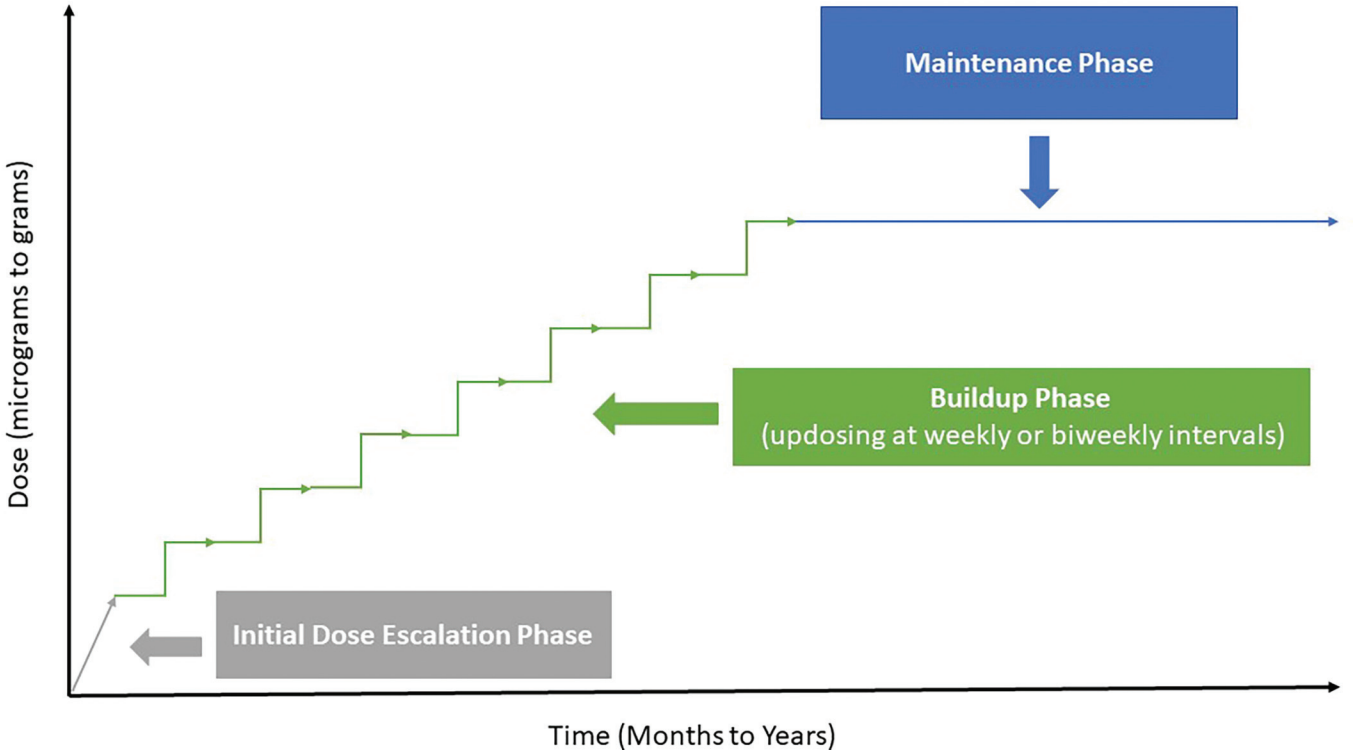

Figure 1. *Typical approach of oral immunotherapy (OIT) protocols. Most OIT protocols consist of three different phases: initial dose escalation (IDE), buildup, and maintenance phase.*

protocol.[6] All the participants in this study successfully proceeded through the buildup phase, which consisted of dose increases every 2 weeks.[6] The three-phase protocol used in this study served as a framework for standardizing contemporary OIT protocols.[6] The first open-label clinical OIT trial for peanut allergy was published in 2009 and followed a similar three-phase protocol, with dosing intervals every 2 weeks during the buildup phase.[7] These initial studies provided the foundation for subsequent multicenter, randomized, placebo controlled clinical trials for OIT. In November 2018, the largest phase III clinical trial for peanut OIT, conducted across 10 countries was published by the Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization (PALISADE) group of clinical investigators.[8] This landmark study paved the way for U.S. Food and Drug Administration (FDA) approval of Palforzia (Aimmune Therapeutics, Brisbane, CA) in January 2020 for children and adolescents with peanut allergy ages 4 to 17 years of age.

OIT PROTOCOL AND DEFINITIONS

The concept of OIT involves ingesting the allergenic food in gradually increasing amounts, with the goal of raising the threshold dose that will provoke a reaction. The types of foods used in OIT vary, depending on the protocol, and may range from natural forms of the food that are readily available in a grocery store to manufactured products (*e.g.*, egg white powder).[9] The protein content of these foods is determined by the U.S. Department of Agriculture package level. OIT has been performed by using nonproprietary food products in community practices for more than a decade.[9] Recently, the advent of Palforzia provides a regulatory approved option for performing peanut OIT in clinical practice; however, an FDA-approved product does not currently exist for any other food.

The majority of OIT protocols follows a similar pattern, which consists of three distinct phases: initial dose escalation (IDE), a gradual buildup, and a maintenance phase (Fig. 1). The IDE phase typically starts with very small doses of food protein in the range of micrograms (*e.g.*, 10–500 μg) that are quickly increased to a maximum of 10–25 mg of food protein.[10] The IDE phase takes place over 5–10 doses on day 1 of the protocol, with the goal of identifying the highest subthreshold dose that is tolerable for home administration. A few protocols used in clinical practice have lower starting doses (*e.g.*, 2.5 μg of peanut protein), followed by escalating doses until a target dose of 2.05 mg of peanut protein is achieved on the initial day.[11] Alternatively, some OIT protocols use a subthreshold fixed dose on day 1 instead of an IDE phase for ease of administration.[10]

During the buildup phase, doses are increased in increments of 25% to 100% at weekly or every two week intervals under medical supervision. Home doses are continued daily in between dose escalation visits. This

Table 1 **Food immunotherapy terms and definitions**

Term	Definition
Eliciting dose	The single dose (in milligrams of food protein) that leads to objective signs or symptoms of an immediate hypersensitivity reaction and results in termination of food challenge
Successfully consumed dose	The single highest dose (in milligrams of food protein) that is tolerated without dose-limiting symptoms
Cumulative reactive dose	The sum of all the doses consumed (in milligrams of food protein), including the eliciting dose
Cumulative tolerated dose	The sum of all the doses (in milligrams of food protein) consumed up to the successfully consumed dose

process is continued for several weeks to months until the maintenance dose is reached. Maintenance dosing may vary considerably, depending on the food protein and the published study, with the length of treatment ranging from months to years.[12] For peanut, maintenance dosing may range from 300 to 5000 mg of peanut protein per day. Maintenance dosing for milk ranges from 4500 to 7200 mg of milk protein, whereas target maintenance dosing for egg is ~5000 mg of egg protein.[13]

The overall aim of OIT is to induce desensitization and, possibly, tolerance to an allergenic food. Desensitization refers to the temporary increase in the threshold of the food protein required to trigger an allergic reaction while on active therapy.[14] OIT has been shown to be effective at inducing desensitization, particularly in children, which may mitigate risks of accidental exposures, and, in turn, this perceived benefit may improve perceptions on quality of life.[15] Although the ultimate goal of OIT is to develop tolerance, defined as permanent resolution of clinical reactivity to any amount of the allergen, this has been challenging to measure in clinical trials.[14] Alternatively, some OIT studies assessed "sustained unresponsiveness" as an indicator of clinical efficacy.[16–18] Sustained unresponsiveness refers to the ability to tolerate the dietary allergen with no evidence of clinical reactivity after a short period (*e.g.,* weeks to months) of therapy discontinuation.[15]

Per (PRACTALL (Practical Allergy) guidelines,[19] a joint initiative of the American Academy of Allergy, Asthma and Immunology, and the European Academy of Allergy and Clinical Immunology to standardize food challenges, most OIT clinical trials perform double-blind, placebo-controlled food challenges (DBPCFC) at enrollment to confirm reactivity and at study conclusion to assess for therapeutic outcomes. Specific terminology has been designated to describe certain clinical end points during DBPCFCs and is summarized in Table 1.[20] Understanding the nuances in terminology is imperative for interpreting the results of challenges and for determining which end points are most clinically relevant for patients.

OIT EFFICACY AND SAFETY

OIT has been studied in clinical trials for a variety of foods, including milk, egg, peanut, wheat, sesame, baked milk, and baked egg.[14] The most robust clinical evidence of desensitization has been reported in children for peanut, milk, and egg OIT, whereas a subset of studies demonstrated sustained unresponsiveness with egg and peanut OIT.[14,20] The effects of OIT on immune modulation include decreased mast cell and basophil activation, decreased food-specific IgE and increased IgG4 antibodies.[14] Despite a repertoire of data in favor of OIT efficacy, adverse reactions associated with OIT may be a limiting factor for a subset of patients. Most of the reactions are limited to the oropharynx (*e.g.,* oral itching) and are more frequent during the IDE and buildup phases; however, anaphylaxis has been reported during maintenance dosing.[15] Some of the risk factors that raise the probability of a systemic reaction include exercise, infection, and menses.[10] These risk factors are usually addressed by counseling patients with regard to timing of physical activity and dose adjustments during acute illness. In 2014, a meta-analysis suggested that eosinophilic esophagitis may develop in up to 2.7% of patients on milk, peanut, or egg OIT;[21] however, whether OIT directly causes eosinophilic esophagitis remains to be elucidated.[15] Given these limitations, OIT may not be the optimal treatment for some patients and underscores the importance of exploring alternative approaches.

EPIT

EPIT is another novel strategy for treating food allergies that involves applying an adhesive patch that contains small doses of food protein, ~250 μg, onto the patient's intact skin. Clinical EPIT trials in the United States have used the Viaskin Peanut patch created by DBV Technologies (Montrouge, France), which relies on moisture from the skin to collect under the patch and solubilize the antigen. The solubilized antigen is then directly presented to dendritic cells in the

Table 2 **Comparison of food allergen immunotherapy treatment approaches**

	Oral Immunotherapy	Epicutaneous Immunotherapy	Sublingual Immunotherapy
Route of therapy	Ingested	On the skin	Under the tongue
Allergens studied in clinical trials	Peanut, milk, egg, wheat, sesame, baked milk, and baked egg	Peanut and milk	Peanut, milk, hazelnut, peach, and kiwi
Maintenance dose	300–4000 mg	250 μg	1–10 mg
Localized adverse effects	Most commonly oropharyngeal or gastrointestinal symptoms	Most commonly skin symptoms	Most commonly oropharyngeal symptoms
Systemic adverse effects	Less common overall; risk factors include physical activity, acute illness, and menses	Rarely occur	Rarely occur
Desensitization	Strong efficacy	Moderate efficacy	Moderate efficacy
Regulatory approval	Approved for peanut allergy	Application rejected due to patch adhesion concerns	Not submitted

epidermis, initiating a cascade of immune responses.[20] A proposed advantage of this method is the favorable safety profile because the epidermis is not vascularized, which minimizes the risk for systemic absorption of the allergen. In contrast to OIT, maintenance dosing is easily achieved once the patch is worn for 24 hours and does not require specific precautions in the case of acute illness (Table 2).

Although EPIT is under investigation for milk and peanut allergy, the most advanced clinical trials have focused on peanut allergy.[22,23] In Peanut EPIT Efficacy and Safety (PEPITES), a phase III, multicenter, double-blind, placebo controlled trial, >350 children ages 4 to 11 years with peanut allergy were randomized to receive a 250-μg patch or placebo for 12 months. Response to treatment, depending on the baseline reactive dose, was defined as either a reactive dose of ≥300 mg or ≥10,000 mg of peanut protein at exit challenge. The difference in clinical response between the treatment and placebo groups was statistically significant; however, due to the high response rate in the placebo group (35.3% in the treatment group versus 13.6% in the placebo group), the study did not meet the predetermined lower bound of the confidence interval required for the study's primary end point.[22] Patch-site reactions of mild-to-moderate severity that decreased over time were the most frequently reported adverse events.

In the PEPITES Open-Label Extension (PEOPLE) study, an open-label extension of PEPITES, 51.8% of the participants achieved an eliciting dose of >1000 mg at month 36 compared with 40.4% at 12 months with a similar favorable safety profile. There is considerable evidence to suggest that EPIT is safe with modest efficacy, especially when used long-term, and may be a suitable alternative for patients who are not ideal candidates for OIT.[23] Food allergy quality of life was prospectively measured by using validated questionnaires, the Food Allergy Quality of Life Questionnaire (FAQLQ) parent form (PF) and FAQLQ-child form (CF) during the PEPITES trial and PEOPLE trial.[22,23] There was a significant FAQLQ-PF improvement in the participants initially randomized to treatment who met the efficacy primary end point and in the participants with any eliciting dose increase at 24 months.[24] Despite these promising results on safety, efficacy, and positive impact on quality of life, the Viaskin Peanut patch is not yet approved by the FDA.

SLIT

Compared with OIT and EPIT, SLIT is in earlier stages of investigation. This technique involves holding the allergen in liquid form under the tongue for a few minutes before swallowing. Immune tolerance is achieved when the allergen is engulfed by dendritic cells in the oral mucosa and presented to T lymphocytes in proximal lymph nodes and, more recently, it is thought that IgA may also play a role by exhibiting an anti-inflammatory effect and influencing the immune response.[25,26] SLIT is similar to OIT in regard to buildup and maintenance phases; however, SLIT protocols do not have an IDE phase and the maintenance doses for SLIT are typically lower, in the range of 1–10 mg of food protein.[14]

Although clinical SLIT trials have been conducted for hazelnut, milk, peach, and kiwi allergies, most studies have focused on peanut allergy.[14,27–30] The first clinical trial for peanut SLIT was published in 2011

and involved 18 children, 1–11 years of age, at a single site, who were randomized to receive 12 months of SLIT with either peanut protein or placebo.[26] The treatment group safely tolerated 20 times more peanut protein than the placebo group did during the DBPCFC at study conclusion, with most of the dosing adverse effects limited to the oropharynx.[26] However, a limitation of this study was the small sample size and lack of baseline entry challenges. A multicenter study in a peanut SLIT cohort, which consisted of 40 participants, ages 12 to 40 years, showed modest clinical desensitization after 44 weeks of therapy.[31]

A long-term follow-up study of the same cohort also demonstrated modest desensitization after 3 years of SLIT therapy; however, a large proportion of the participants withdrew from the study.[32] In 2019, 48 children with peanut allergy, ages 1 to 11 years, underwent extended treatment with peanut SLIT.[33] Approximately 87% of the participants who completed 3 to 5 years of peanut SLIT successfully tolerated ≥ 750 mg of peanut protein during the exit DBPCFC. Overall, SLIT was well tolerated in this long-term study, with adverse effects reported in 4.78% of all doses, and transient oropharyngeal itching was the most common symptom. Most symptoms self-resolved, and none required epinephrine. Two participants withdrew from the study due to gastrointestinal symptoms, with complete resolution of symptoms after stopping therapy.[33] SLIT studies in children have shown promising results in regard to efficacy and safety;[26,33] however, additional clinical studies in larger cohorts are needed to hone in on long-term efficacy and determine the appropriate patient selection for this therapy.

CONCLUSION

Substantial progress in the field of food allergy research in the past 2 decades has led to a new era in food allergy management, with multiple novel approaches on the horizon. Of these emerging therapies, OIT is the most advanced in development, with robust data on efficacy; however, clinical use of OIT may be limited by the risk of adverse reactions. Conversely, EPIT has shown more moderate clinical effects with a favorable safety profile, but it has not reached the stage of achieving FDA approval. Clinical studies that involve SLIT have demonstrated modest efficacy with minimum adverse effects; however, additional studies are needed to clarify the ideal patient population and long-term outcomes. None of these therapeutic modalities studied to date provide a cure for food allergy; however, these therapies may provide a protective buffer from accidental ingestions in patients who adhere to consistent, long-term therapy.

Next-generation therapies for the treatment of food allergies include the use of biologics as monotherapy or as an adjunct to OIT, DNA vaccines, and peptide immunotherapy. Although the details of these novel therapeutics are beyond the scope of this review, these innovative approaches suggest a paradigm shift in food allergy management away from strict avoidance as the only intervention to active treatment. It is crucial for providers to be informed of these new developments and take a patient-centered approach when evaluating potential treatment options.

CLINICAL PEARLS

- Of the emerging therapeutic modalities for the treatment of food allergies, OIT is the most well-studied therapy, with robust evidence on clinical efficacy demonstrated in children for peanut, milk, and egg OIT.
- Both SLIT and OIT protocols have buildup and maintenance phases; however, only OIT has an IDE phase and the maintenance doses for OIT are much higher compared with SLIT.
- Clinical EPIT trials have focused on peanut allergy and have demonstrated moderate efficacy with a favorable adverse effect profile; however, it has not yet reached the stage of regulatory approval.

REFERENCES

1. Oppenheimer JJ, Nelson HS, Bock SA, et al. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol. 1992; 90:256–262.
2. Scholfield AT. A case of egg poisoning. Lancet. 1908; 171:716.
3. Patriarca C, Romano A, Venuti A, et al. Oral specific hyposensitization in the management of patients allergic to food. Allergol Immunopathol (Madr). 1984; 12:275–281.
4. Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. Aliment Pharmacol Ther. 2003; 17:459–465.
5. Meglio P, Bartone E, Plantamura M, et al. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. Allergy. 2004; 59:980–987.
6. Buchanan AD, Green TD, Jones SM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. J Allergy Clin Immunol. 2007; 119:199–205.
7. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009; 124:292–300, 300.e1-e97.
8. PALISADE Group of Clinical Investigators; Vickery BP, Vereda A, et al. AR101 oral immunotherapy for peanut allergy. N Engl J Med. 2018; 379:1991–2001.
9. Wasserman RL, Jones DH, Windom HH. Oral immunotherapy for food allergy: the FAST perspective. Ann Allergy Asthma Immunol. 2018; 121:272–275.
10. Wasserman RL, Factor J, Windom HH, et al. An approach to the office-based practice of food oral immunotherapy. J Allergy Clin Immunol Pract. 2021; 9:1826–1838.e8.
11. Wasserman RL, Hague AR, Pence DM, et al. Real-world experience with peanut oral immunotherapy: lessons learned from 270 patients. J Allergy Clin Immunol Pract. 2019; 7:418–426.e4.
12. Wood RA. Food allergen immunotherapy: current status and prospects for the future. J Allergy Clin Immunol. 2016; 137:973–982.
13. Begin P, Chan ES, Kim H, et al. CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral

immunotherapy in IgE-mediated food allergy. Allergy Asthma Clin Immunol. 2020; 16:20.
14. Scurlock AM, Shreffler WG. *Immunotherapeutic approaches to the treatment of food allergy*. In: Pediatric Allergy Principles and Practice. DYM Leung, C Akdis, L Bacharier, et al (Eds). Elsevier Health Sciences United States: , 308–317, 2020.
15. Anvari S, Anagnostou K. The nuts and bolts of food immunotherapy: the future of food allergy. Children (Basel). 2018; 5:47.
16. 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.
17. 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.e8.
18. Patil SU, Steinbrecher J, Calatroni A, et al. Early decrease in basophil sensitivity to Ara h 2 precedes sustained unresponsiveness after peanut oral immunotherapy. J Allergy Clin Immunol. 2019; 144:1310–1319.e4.
19. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. J Allergy Clin Immunol. 2012; 130:1260–1274.
20. Kim EH, Burks AW. Food allergy immunotherapy: oral immunotherapy and epicutaneous immunotherapy. Allergy. 2020; 75:1337–1346.
21. 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.
22. 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.
23. Fleischer DM, Shreffler WG, Campbell DE, et al. Long-term, open-label extension study of the efficacy and safety of epicutaneous immunotherapy for peanut allergy in children: PEOPLE 3-year results. J Allergy Clin Immunol. 2020; 146:863–874.
24. DunnGalvin A, Fleischer DM, Campbell DE, et al. Improvements in quality of life in children following epicutaneous immunotherapy (EPIT) for peanut allergy in the PEPITES and PEOPLE studies. J Allergy Clin Immunol Pract. 2021; 9:216–224.e1.
25. Kulis M, Saba K, Kim EH, et al. Increased peanut-specific IgA levels in saliva correlate with food challenge outcomes after peanut sublingual immunotherapy. J Allergy Clin Immunol. 2012; 129:1159–1162.
26. 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.e1.
27. 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. J Allergy Clin Immunol. 2005; 116:1073–1079.
28. 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, 455.e1-5.
29. Fernández-Rivas M, Garrido Fernández JA, Nadal A, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. Allergy. 2009; 64:876–883.
30. Mempel M, Rakoski J, Ring J, et al. Severe anaphylaxis to kiwi fruit: Immunologic changes related to successful sublingual allergen immunotherapy. J Allergy Clin Immunol. 2003; 111: 1406–1409.
31. 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.e1-e7.
32. 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; 135:1240–1248. e1-e3.
33. Kim EH, Yang L, Ye P, et al. Long-term sublingual immunotherapy for peanut allergy in children: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2019; 144:1320–1326.e1. □