

Interventional Therapies for the Treatment of Food Allergy



Christopher P. Parrish, MD^a, Edwin H. Kim, MD, MS^b,
J. Andrew Bird, MD^{c,*}

KEYWORDS

- Food allergy treatment • IgE-mediated food allergy • Oral immunotherapy • OIT
- Sublingual immunotherapy • SLIT • Epicutaneous immunotherapy • EPIT

KEY POINTS

- Approved treatment of IgE-mediated food allergy is currently limited to allergen avoidance and emergency treatment with epinephrine on accidental ingestion.
- Oral immunotherapy has shown promise in recent studies. Most patients achieve successful desensitization but adverse effects are common, including gastrointestinal symptoms and anaphylaxis.
- Sublingual immunotherapy and epicutaneous immunotherapy seem to offer improved safety profiles but lower efficacy.

Food allergy is an increasingly common problem, with an estimated prevalence of up to 8% among young children and 3% to 6% of the entire US population.^{1–3} In recent decades, prevalence has increased, especially for peanut allergy.^{3,4} The natural history of food allergy leads to natural tolerance for some children, but allergies to peanuts and tree nuts usually persist into adulthood.⁵ Milk and egg allergy may also persist, especially among those most severely affected.^{6,7} Although life-threatening anaphylactic reactions to foods do occur, overall mortality due to food allergy is rare.⁸ Evidence is ample, however, that food allergy has a significant impact on

Disclosure Statement: Dr J.A. Bird has received research, travel support, and lecture fees from Aimmune therapeutics and DBV technologies. Dr E.H. Kim has received research, travel support, and honoraria from Aimmune therapeutics and DBV technologies.

^a Food Allergy Center at Children's Medical Center, 1935 Medical District Drive, Dallas, TX 75235, USA; ^b Division of Rheumatology, Allergy and Immunology, University of North Carolina-Chapel Hill, 3300 Thurston Building, Campus Box 7280, Chapel Hill, NC 27599-7280, USA; ^c Departments of Pediatrics and Internal Medicine, Division of Allergy and Immunology, The University of Texas Southwestern Medical Center, 5323 Harry Hines Boulevard, Dallas, TX 75390-9063, USA

* Corresponding author.

E-mail address: Drew.Bird@UTSouthwestern.edu

Immunol Allergy Clin N Am 38 (2018) 77–88

<https://doi.org/10.1016/j.iac.2017.09.006>

0889-8561/18/© 2017 Elsevier Inc. All rights reserved.

immunology.theclinics.com

affected individuals and family members, through morbidity and negative effects on quality of life.^{9,10} Approved management of food allergy is limited to allergen avoidance and administration of rescue medications, such as antihistamines and self-injectable epinephrine as needed when reactions occur. Together, all these factors illustrate the need for an effective therapy for food allergy.

Although reports of successful oral immunotherapy (OIT) for food allergy date to at least 1908,¹¹ this approach was never widely adopted. In the 1990s, attempts to desensitize or promote tolerance through subcutaneous immunotherapy did show increased tolerance to oral peanut challenge, but rates of severe reactions were unacceptably high.^{12,13} Interest in interventional therapies for food allergies has increased recently, with substantial research efforts undertaken to investigate multiple forms of immunotherapy (oral, sublingual, and epicutaneous). Although the Food and Drug Administration (FDA) has not yet approved any interventional therapy for food allergy, this article reviews the progress to date and discusses future prospects in the search for safe, reliable treatment options for food allergy.

IMMUNOTHERAPY

Oral Immunotherapy

OIT has received more attention and currently has a larger evidence base than sublingual immunotherapy (SLIT) or epicutaneous immunotherapy (EPIT). Protocols vary, but the general approach typically involves 3 phases:

- Initial escalation
- Buildup
- Maintenance

Initial escalation dosing is generally performed in a single day with 6 to 8 increasing doses. Doses usually start at less than 1 mg and increase to several milligrams. In the buildup phase, patients ingest a daily dose of the food allergen, which is increased at regular intervals until reaching the target dose. This dose (typically several hundred milligrams or more) is then continued for the duration of the maintenance phase. An oral food challenge (OFC) at the end of maintenance assesses for desensitization, a temporary state of immune unresponsiveness with an increased threshold of reactivity. For those who are successfully desensitized, an additional OFC may be done after a period of abstinence to assess for sustained unresponsiveness (SU). Many patients are desensitized during OIT, but fewer seem to achieve SU, although this has not been significantly addressed in most published studies.

Peanut oral immunotherapy

Interest in peanut OIT has increased significantly, beginning with case reports of successful peanut OIT published in 2006.^{14,15} The first multicenter randomized peanut double-blind placebo-controlled (DBPC) peanut OIT study was reported in 2011.¹⁶ Sixteen of 19 children (age 1–16) in the active treatment arm achieved desensitization, passing a 5000-mg peanut DBPC food challenge (DBPCFC) after 48 weeks OIT with a maintenance dose of 4000-mg peanut protein. The other 3 subjects withdrew due to allergic side effects.

SU after peanut OIT was first reported by Vickery and colleagues¹⁷ in 2014. In this open-label peanut OIT trial, children (age 1–16) were treated for up to 5 years with a peanut OIT maintenance dose of up to 4 g peanut protein per day. Twelve of 24 patients who completed the protocol achieved SU (passed 5 g OFC) 1 month after stopping OIT. Those who passed had lower levels at baseline and at time of challenge of

skin prick test (SPT) wheal size, peanut-specific, Ara h 1–specific, and Ara h 2–specific IgE, and peanut-specific IgE/total IgE ratio.

In a study designed primarily to compare peanut OIT to peanut SLIT, only 63% of patients by intention-to-treat analysis in the OIT group (maintenance dose 2000 mg of peanut protein for 12 months) achieved desensitization, with only 27% achieving 4-week SU.¹⁸ Understanding the correct amount of time to measure allergen abstinence to properly assess prolonged SU is still an area of uncertainty, and it is apparent that SU may be lost with continued avoidance. In 1 study, 7 of 20 patients achieved 3-month SU, but only 4 of 20 maintained SU after an additional 3 months.¹⁹ This loss of SU was associated with reversal of epigenetic changes in regulatory T cells.

The results of the Learning Early about Peanut Allergy study suggest early introduction of peanut is effective for secondary prevention of peanut allergy in high-risk infants already sensitized to peanut,²⁰ which raises the possibility of an early window during which OIT may be more effective. In a randomized, double-blind trial of high-dose versus low dose OIT for 3 years in preschool children (age 9–36 months), 29 of 37 children (78%) overall achieved 4-week SU, with an SU rate of 91% (29 of 32) in per protocol analysis.²¹ It remains unclear if the earlier timing of intervention is responsible for the high SU rate or if other factors, such as lower peanut-specific IgE, are more important. Further studies are needed to further evaluate the influence of age on peanut OIT outcomes. There was no significant difference in efficacy or safety between the 3000-mg and 300-mg dose in these young children. Phase III clinical trials of a commercial peanut OIT product (NCT02635776) are ongoing.

Milk oral immunotherapy

The first 2 reported studies of milk OIT showed desensitization rates of 65.5% and 100%, respectively.^{22,23} In a pilot study, 6 months of milk OIT allowed 72% of children to tolerate a target dose of 200 mL of cow's milk daily, with 3 additional children able to tolerate 40 mL to 80 mL daily.²⁴ Multiple subsequent uncontrolled case series showed desensitization for most patients.^{25–27} The first randomized controlled trial (RCT) of milk and egg OIT showed desensitization rates of 64% in the OIT group and 35% in the control group, with 2-month SU of 36% in the OIT group.²⁸ A year later, the first randomized placebo-controlled study of milk OIT was published by Skripak and colleagues,²⁹ with a median increase in OFC threshold from 40 mg to 5140 mg after 13 weeks OIT with a 500-mg milk protein maintenance dose. Open-label follow-up showed that the maximum dose was successfully escalated to a median of 7000 mg daily (range 1000 mg to 16,000 mg).³⁰ Thirteen of 15 patients underwent OFC, with 6 tolerating 16,000 mg and 7 reacting at doses from 3000 mg to 16,000 mg.

Keet and colleagues³¹ open-label RCT of milk OIT versus milk SLIT showed superior rates of desensitization with OIT, but 6-week SU was achieved in only 40% by intention-to-treat analysis, with 2 patients losing desensitization after only 1 week of abstinence from therapy. Long-term follow-up of the studies by Skripak and colleagues²⁹ and Keet and colleagues³¹ showed that less than a third fully tolerated milk 3 years to 5 years after completing OIT.³² Although most studies include daily maintenance doses, no significant difference in efficacy was found between daily and twice-per-week maintenance dosing while allowing other milk products freely in the diet,³³ but this was based on tolerance of maintenance doses, not OFC assessment of desensitization or SU.

Egg oral immunotherapy

Early studies of egg OIT showed desensitization in a majority of patients in small case series.^{22,23} Five of 7 (71%) patients passed an 8-g OFC after 24 months' egg OIT with

300-mg egg white protein, but only 2 (29%) achieved 3-month SU.³⁴ In a follow-up study with individualization of OIT dose (median dose 2400 mg), 6 of 8 (75%) achieved 4-week SU.³⁵ The first DBPC randomized multicenter study of egg OIT was published in 2012. In children 5 to 11 years of age with a maintenance dose of 2-g egg-white powder daily, 30 of 40 (75%) were desensitized (passed 10-g egg-white powder OFC) at 22 months, but only 11 (27.5%) had SU 6 weeks to 8 weeks later.³⁶ Long-term follow-up showed that 4-week to 6-week SU increased to 50% (20 of 40) by 4 years.³⁷ Recent studies have shown SU of 31% to 37% after shorter durations of treatment.^{38,39}

Multiple-food Oral Immunotherapy

Although single foods are the target for most OIT trials, as many as 30% of children with food allergy react to multiple foods, and this subset of children tends to have more persistent food allergy.² This lower likelihood of natural food allergy resolution increases the desire for effective treatment. A phase 1 pilot study of multiple-food OIT (peanut and up to 4 other foods) showed no significant difference in adverse events (AEs) versus peanut OIT alone.⁴⁰ Results were similar with omalizumab pretreatment and rush OIT to multiple foods.⁴¹ Further studies on multiple-food OIT are needed to clarify its efficacy, risks, and benefits.

Adverse Reactions to Oral Immunotherapy

Although OIT has been shown to effectively desensitize a majority of patients and even produce SU or tolerance in some, concerns remain regarding the safety of OIT. AEs of concern include IgE-mediated cutaneous, respiratory, and multisystem reactions ranging from hives or wheezing to anaphylaxis. A significant subset of subjects experience isolated gastrointestinal (GI) symptoms (abdominal pain, nausea, vomiting, and dysphagia) with eosinophilic esophagitis (EoE) diagnosed in some. The evaluation of the safety of OIT is limited by the relative lack of large studies focused on detailed assessment of safety.

The largest analysis of peanut OIT safety published to date is a retrospective analysis of pooled data from 3 pediatric peanut OIT trials,^{16,17,42} which found that 80% of 104 patients experienced mild (85%) to moderate (15%) treatment-related AEs during OIT.⁴³ Reactions were experienced by 72% of patients during buildup and 47% during maintenance, with reaction rates of 2.8 per 100 dosing days during buildup and 0.4 per 100 dosing days during maintenance. The vast majority (91% during buildup and 99% during maintenance) of reactions occurred at home. Treatment of the AEs was required by 61% of subjects, representing 22% of all AEs, with 93% of these occurring at home.

Risk Factors for Reactions

Infection, exercise, and pollen allergy have been identified as factors that can lead to decreased reactivity threshold and increased AEs during milk and egg OIT.²⁸ These augmentation factors were also seen with home dosing during peanut OIT, with sub-optimal control of asthma, menstruation, and dose ingestion on an empty stomach identified as additional factors.⁴⁴ Protocol adjustments, such as holding doses while acutely ill, ensuring asthma control, dosing within 2 hours of a meal or snack, and avoiding exercise for at least 2 hours after dosing seem to reduce AEs. Factors associated with reactions during peanut OIT in clinical practice also included exercise after dosing, viral illness, uncontrolled asthma, delay in dosing, and not eating other food with doses.⁴⁵ Virkud and colleagues⁴³ identified comorbid allergic rhinitis as a predictor of AEs, especially reactions during maintenance phase or during peak pollen months. Increased peanut SPT wheal size was associated with a slight overall

increase in AEs, which was statistically significant in buildup but not maintenance phase. Asthma was associated with a significantly higher risk of reaction only during maintenance phase. Peanut SPT wheal size was also independently associated with isolated GI symptoms.

Gastrointestinal Reactions and Eosinophilic Esophagitis

GI reactions (abdominal pain, nausea, vomiting, and dysphagia) are common in OIT.^{46–49} Although most patients do not undergo endoscopy during OIT, a meta-analysis noted 20 patients from 12 different reports who developed EoE during OIT with milk, peanut, egg, and baked milk, for an estimated prevalence of EoE in OIT of 2.7%.⁵⁰ In a clinical practice setting, the reported rate of persistent isolated GI symptoms was 4.5%, with no comment on endoscopic evaluation or EoE,⁴⁵ but an earlier abstract by the same group reported 4 cases of EoE in 75 OIT patients.⁵¹ In the large analysis by Virkud and colleagues,⁴³ 49% of patients experienced GI symptoms, 33% of all AEs included GI symptoms, and 26% of AEs involved isolated GI symptoms. Ten of 13 patients who withdrew from OIT due to persistent OIT-related symptoms did so because of GI symptoms (abdominal pain, emesis, and dysphagia), representing 10% of the overall population and 77% of symptomatic withdrawals. Three of these patients underwent esophagogastroduodenoscopy, and 2 of them had findings consistent with EoE. Peanut SPT wheal size was the only factor significantly associated with isolated GI symptoms (1.8-fold increase in risk for each 5-mm increase in SPT wheal). A single-center analysis of 794 subjects receiving milk, peanut, egg, and sesame OIT found recurrent GI symptoms (3 or more episodes per month of abdominal pain and/or vomiting) in 8.2% (65 patients).⁵² These GI symptoms were associated with higher baseline peripheral eosinophil counts, greater increase in eosinophil counts, and higher maximum eosinophil counts, so the investigators termed the association, *OIT-induced gastrointestinal and eosinophilic responses*. Symptoms resolved and absolute eosinophil counts significantly decreased with reduction or cessation of dosing, and symptoms did not recur for 42 of 45 patients who resumed dosing. Only 3 patients underwent endoscopy, with all 3 showing EoE. It remains unclear what proportion of patients with significant GI symptoms during OIT would have EoE on biopsy, because endoscopy may be more likely to be pursued in those with more severe or persistent symptoms.

Anti-IgE therapy has been ineffective in EoE, and the finding that 2 of 27 omalizumab-treated peanut OIT subjects in a recent trial had symptoms consistent with EoE (biopsy proved in 1) suggests that although anti-IgE therapy may improve the overall safety profile of OIT, it may be ineffective in preventing OIT-induced EoE.⁵³ Although this hints at shared pathophysiology between EoE and OIT-induced GI symptoms, some features of OIT-induced GI symptoms are atypical of EoE, such as lack of male predominance and the ability of many patients to resume and successfully continue desensitization without return of symptoms. It is also unclear whether cases of EoE during OIT represent new-onset EoE triggered by OIT or, alternatively, recognition of preexisting EoE that had not been diagnosed prior to OIT.

Sublingual Immunotherapy

SLIT is an alternative mode of immunotherapy that offers convenience and potentially an improved safety profile. For years, it has been widely accepted in Europe for seasonal allergic rhinitis, and FDA-approved products for treatment of seasonal allergic rhinitis have recently been introduced in the United States. Mechanistic work by Allam and colleagues⁵⁴ has suggested involvement of protolerogenic Langerhans cells in the

oral mucosa that ultimately leads to the desensitization and potential tolerance-inducing effect. There are far fewer studies on SLIT for the treatment of food allergy than for OIT, and the majority have been published within the last decade. SLIT has been investigated as treatment of allergies to hazelnut, peach, and milk, and although only 3 separate trials have used peanut SLIT, this is the most reported food allergy treated with SLIT.^{18,31,55–58} SLIT protocols deliver no more than several milligrams of protein at maintenance whereas OIT protocols build up to a maintenance dose of several hundred milligrams or several grams of protein. SLIT protocols typically use a biweekly buildup phase and a maintenance phase without the initial dose escalation day because of the lower amount of allergen given compared with OIT. Similar to OIT, OFCs after a set period of treatment and after a period of SLIT avoidance have been used to assess desensitization and SU respectively.

In the first double-blind study of peanut SLIT, using a dose of 2 mg of peanut protein daily, Kim and colleagues⁵⁷ demonstrated a significant increase in reaction threshold for subjects on peanut SLIT compared with those on placebo (1710 mg vs 85 mg) after 12 months of therapy. Safety was excellent with 12% of doses resulting in symptoms (compared with 9% on placebo) and most symptoms consisting of transient oropharyngeal itching.

In the first multicenter trial of peanut SLIT, Fleischer and colleagues⁵⁹ studied the efficacy of peanut SLIT in peanut-allergic teenagers and adults. After 44 weeks, 70% of subjects on peanut SLIT were responders as defined by at least a 10-fold increase in successfully consumed dose (SCD) compared with 15% in the placebo group. The results were more modest, however, than in the single-center Kim and colleagues trial, because the median SCD was 496 mg. Long-term follow-up of this cohort demonstrated 8-week SU in only 11% of subjects and, despite the presumed convenience of SLIT, greater than 50% of subjects withdrew from the study.⁵⁸

Finally, in a study of OIT versus SLIT for peanut allergy, similar to the Consortium of Food Allergy Research results, Narisety and colleagues¹⁸ demonstrated at least a 10-fold increase in reaction threshold in 70% of subjects treated with peanut SLIT for 12 months and a median reaction threshold of 496 mg. In this head-to-head study, it was noteworthy that the change in the threshold of reactivity with peanut SLIT (22-fold) was far less than that seen with peanut OIT (141-fold) although peanut SLIT seemed more tolerable.

Overall, peanut SLIT has shown promise as a safe alternative to OIT, with significant but more modest increases in reaction threshold and corresponding immunologic changes demonstrating modulation of the immune response. Ongoing studies of peanut SLIT hope to broaden our understanding of the therapy by examining the SU effect in more depth (NCT01373242) and investigating its effect in a younger population of 1 to 4 year olds (NCT02304991).

Epicutaneous Immunotherapy

Another approach with a favorable safety profile is to deliver the allergen through the skin. EPIT was first reported for the treatment of allergic asthma in the 1950s by Pau-trizel and colleagues,⁶⁰ who used drops of allergen extracts on scarified skin.⁶⁰ Recently, the development of a new epidermal delivery system (Viaskin, DBV Technologies, Montrouge, France) has allowed for administration of allergens through intact skin. This technology uses a central polyethylene membrane charged with electrostatic forces to create an occlusive chamber on the skin, leading to condensation within the chamber and subsequent solubilization and epicutaneous absorption of allergen through intact skin. The allergen is taken up by dendritic cells in the stratum corneum, internalized, and then transported to regional draining lymph nodes.⁶¹

Table 1
Food immunotherapy treatment summaries

	Oral Immunotherapy ^{16–21,49–52}	Sublingual Immunotherapy ^{57–59}	Epicutaneous Immunotherapy ⁶³
Maintenance dose	300 mg–4000 mg	~ 1 mg–~ 4 mg	50 µg–500 µg
Activity restriction	• Take dose with meal • No activity for ~ 2 h after ingestion • Withhold with illness	• Do not eat for ~ 30 min after dosing	• Do not apply to inflamed skin
Observed dosing?	Up-dosing observed	Up-dosing observed	Initiation and periodic follow-up
Adverse effects	Common mild AEs Frequent GI AEs Anaphylaxis possible	Mouth itching most common (mild) Anaphylaxis rare	Localized irritation at site of patch placement Anaphylaxis not reported
Threshold of reactivity modulation among peanut interventional trials	60%–80% desensitized to 5000 mg with 2000 mg to 4000 mg maintenance dose	1760 mg after 1 y (1–11 years old) 996 mg after 68 wk (12–40 years old)	144 mg after 1 y (more effective 4–11 years old, though trial was not powered to specifically study this age group and threshold changes after more than 1 year of therapy have not yet been reported).

Milk epicutaneous immunotherapy

In a 2010 pilot trial, milk EPIT was well tolerated, with no serious systemic adverse reactions, only local irritation and eczema.⁶² The mean cumulative tolerated dose after 3 months of treatment increased by 12-fold versus 8% in the placebo group ($P = .13$). A combined phase I/II study (NCT02223182) began in 2014 and is ongoing, and milk EPIT is also being investigated in the treatment of milk-induced EoE (NCT02579876).

Peanut epicutaneous immunotherapy

Jones and colleagues⁶³ recently published a multisite, double-blind, placebo-controlled RCT that evaluated doses of 100 μg (VP [Viaskin Peanut] 100) and 250 μg (VP250) in 74 children and young adults (ages 4–25 years). The primary endpoint (passing a DBPCFC with 5044 mg of peanut protein or a 10-fold increase in the SCD at week 52) was achieved by 45.8% of the VP100 group and 48% of the VP250 group compared with 12% in the placebo group. The only participant who passed the 5044 mg OFC was in the placebo group. Post hoc analysis showed that only 12.5% of the VP100 and 28.0% of the VP250 group tolerated at least 1044 mg at week 52. Furthermore, only 8.3% of the VP100 and 16.0% of VP250-treated patients had both a 10-fold increase in SCD and tolerated 1044 mg of protein. Mild local reactions were reported with 79.8% of patch doses compared with 14.4% in the placebo group. Peanut-specific IgG4 levels and IgG4/IgE ratios increased in EPIT-treated participants, and there were nonsignificant trends toward reduced basophil activation and peanut-specific Th2 cytokines. The trial is ongoing and will evaluate whether prolonged therapy induces a higher threshold of reactivity.

Initial studies have shown general tolerability and safety but modest efficacy of EPIT for peanut allergy, and further studies are ongoing with a commercial product (NCT02636699) currently in phase 3 clinical trials.

SUMMARY

Research into interventional therapies for IgE-mediated food allergy has accelerated rapidly in the past decade. Currently published evidence has shown that a majority of peanut-allergic and milk-allergic children and adolescents are able to achieve desensitization with OIT; however, data have also uncovered an increased risk of experiencing an allergic reaction associated with treatment versus allergen avoidance. This fact underscores the importance of taking a measured approach in pursuing treatment of food-allergic patients. Questions remain to be answered regarding prolonged treatment with OIT; the likelihood of developing SU; OIT for foods other than milk, peanut, and egg; and appropriate identification of patients who are most likely to respond ideally to OIT. A currently ongoing phase 3 trial for peanut allergy (NCT02635776) will provide additional answers to some of these questions.

Although SLIT and EPIT data are more limited, currently available evidence suggests that although they provide a less robust margin of protection against allergen ingestion, both approaches have a favorable safety profile. It is likely that OIT and EPIT therapies will be available in FDA-approved forms soon and additional treatment options are likely to be available in the next decade. As these products come to the market, allergists need to consider risks, benefits, and patient lifestyle considerations before embarking on a treatment course ([Table 1](#)).

Treatment of food allergy is still in its infancy and studies are needed to examine adjuvants to improve efficacy, comprehensive treatment of multifood allergic patients, the role of biologics to improve safety, and alternative approaches beyond those discussed in this review. It is an exciting time for the field, and the authors are optimistic

that patients with life-threatening food allergies will have a variety of therapeutic options in the near future.

REFERENCES

1. Sicherer SH. Epidemiology of food allergy. *J Allergy Clin Immunol* 2011;127:594–602.
2. Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011;128:e9–17.
3. Sampson HA, Aceves S, Bock SA, et al. Food allergy: a practice parameter update-2014. *J Allergy Clin Immunol* 2014;134:1016–25.e43.
4. Sicherer SH, Munoz-Furlong A, Godbold JH, et al. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. *J Allergy Clin Immunol* 2010;125:1322–6.
5. Wood RA. The natural history of food allergy. *Pediatrics* 2003;111:1631–7.
6. Sicherer SH, Wood RA, Vickery BP, et al. The natural history of egg allergy in an observational cohort. *J Allergy Clin Immunol* 2014;133:492–9.
7. Wood RA, Sicherer SH, Vickery BP, et al. The natural history of milk allergy in an observational cohort. *J Allergy Clin Immunol* 2013;131:805–12.
8. Umasunthar T, Leonardi-Bee J, Hodes M, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin Exp Allergy* 2013;43:1333–41.
9. Cohen BL, Noone S, Munoz-Furlong A, et al. Development of a questionnaire to measure quality of life in families with a child with food allergy. *J Allergy Clin Immunol* 2004;114:1159–63.
10. Leung TF, Yung E, Wong YS, et al. Quality-of-life assessment in Chinese families with food-allergic children. *Clin Exp Allergy* 2009;39:890–6.
11. Schofield AT. A case of egg poisoning. *Lancet* 1908;171:716.
12. Nelson HS, Lahr J, Rule R, et al. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J Allergy Clin Immunol* 1997;99:744–51.
13. Oppenheimer JJ, Nelson HS, Bock SA, et al. Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992;90:256–62.
14. Mansfield L. Successful oral desensitization for systemic peanut allergy. *Ann Allergy Asthma Immunol* 2006;97:266–7.
15. Patriarca G, Nucera E, Pollastrini E, et al. Oral rush desensitization in peanut allergy: a case report. *Dig Dis Sci* 2006;51:471–3.
16. 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;127:654–60.
17. 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;133:468–75.
18. Narisety SD, Frischmeyer-Guerrero 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;135:1275–82.e1–6.
19. Syed A, Garcia MA, Lyu SC, et al. Peanut oral immunotherapy results in increased antigen-induced regulatory T-cell function and hypomethylation of forkhead box protein 3 (FOXP3). *J Allergy Clin Immunol* 2014;133:500–10.

20. Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *New Engl J Med* 2015;372:803–13.
21. 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;139:173–81.e8.
22. Patriarca G, Nucera E, Roncallo C, et al. Oral desensitizing treatment in food allergy: clinical and immunological results. *Aliment Pharmacol Ther* 2003;17: 459–65.
23. Patriarca G, Schiavino D, Nucera E, et al. Food allergy in children: results of a standardized protocol for oral desensitization. *Hepatogastroenterology* 1998; 45:52–8.
24. Meglio P, Bartone E, Plantamura M, et al. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. *Allergy* 2004;59:980–7.
25. Zapatero L, Alonso E, Fuentes V, et al. Oral desensitization in children with cow's milk allergy. *J Investig Allergol Clin Immunol* 2008;18:389–96.
26. Alvaro M, Giner MT, Vazquez M, et al. Specific oral desensitization in children with IgE-mediated cow's milk allergy. Evolution in one year. *Eur J Pediatr* 2012;171: 1389–95.
27. Sanchez-Garcia S, Rodriguez del Rio P, Escudero C, et al. Efficacy of oral immunotherapy protocol for specific oral tolerance induction in children with cow's milk allergy. *Isr Med Assoc J* 2012;14:43–7.
28. Staden U, Rolinck-Werninghaus C, Brewe F, et al. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 2007;62:1261–9.
29. Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008;122:1154–60.
30. Narisety SD, Skripak JM, Steele P, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2009;124:610–2.
31. 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;129:448–55, 55.e1–5.
32. Keet CA, Seopaul S, Knorr S, et al. Long-term follow-up of oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2013;132:737–9.e6.
33. Pajno GB, Caminiti L, Ruggeri P, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol* 2010;105:376–81.
34. 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.
35. Vickery BP, Pons L, Kulis M, et al. Individualized IgE-based dosing of egg oral immunotherapy and the development of tolerance. *Ann Allergy Asthma Immunol* 2010;105:444–50.
36. Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *New Engl J Med* 2012;367:233–43.
37. Jones SM, Burks AW, Keet C, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. *J Allergy Clin Immunol* 2016;137:1117–27.e1–10.
38. Escudero C, Rodriguez Del Rio P, Sanchez-Garcia S, et al. Early sustained unresponsiveness after short-course egg oral immunotherapy: a randomized controlled study in egg-allergic children. *Clin Exp Allergy* 2015;45:1833–43.

39. Caminiti L, Pajno GB, Crisafulli G, et al. Oral immunotherapy for egg allergy: a double-blind placebo-controlled study, with postdesensitization follow-up. *J Allergy Clin Immunol Pract* 2015;3:532–9.
40. Begin P, Winterroth LC, Dominguez T, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. *Allergy Asthma Clin Immunol* 2014;10:1.
41. Begin P, Dominguez T, Wilson SP, et al. Phase 1 results of safety and tolerability in a rush oral immunotherapy protocol to multiple foods using Omalizumab. *Allergy asthma, Clin Immunol* 2014;10:7.
42. 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, e1-97.
43. Virkud YV, Burks AW, Steele PH, et al. Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy. *J Allergy Clin Immunol* 2017;139:882–8.e5.
44. Varshney P, Steele PH, Vickery BP, et al. Adverse reactions during peanut oral immunotherapy home dosing. *J Allergy Clin Immunol* 2009;124:1351–2.
45. Wasserman RL, Factor JM, Baker JW, et al. Oral immunotherapy for peanut allergy: multipractice experience with epinephrine-treated reactions. *J Allergy Clin Immunol Pract* 2014;2:91–6.
46. Anagnostou K, Clark A, King Y, et al. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy* 2011;41:1273–81.
47. 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;383:1297–304.
48. Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010;126:83–91.e1.
49. Yu GP, Weldon B, Neale-May S, et al. The safety of peanut oral immunotherapy in peanut-allergic subjects in a single-center trial. *Int Arch Allergy Immunol* 2012;159:179–82.
50. 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;113:624–9.
51. Wasserman RL, Sugerman RW, Mireku-Akomeah N, et al. Peanut oral immunotherapy (OIT) of food allergy (FA) carries a significant risk of eosinophilic esophagitis (EoE). *J Allergy Clin Immunol* 2011;127:AB28.
52. Goldberg MR, Elizur A, Nachshon L, et al. Oral immunotherapy-induced gastrointestinal symptoms and peripheral blood eosinophil responses. *J Allergy Clin Immunol* 2016;139(4):1388–90.e4.
53. MacGinnitie AJ, Rachid R, Gragg H, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol* 2017;139:873–81.e8.
54. Allam JP, Wurtzen PA, Reinartz M, et al. Phl p 5 resorption in human oral mucosa leads to dose-dependent and time-dependent allergen binding by oral mucosal Langerhans cells, attenuates their maturation, and enhances their migratory and TGF-beta1 and IL-10-producing properties. *J Allergy Clin Immunol* 2010;126:638–45.e1.
55. Enrique E, Malek T, Pineda F, et al. Sublingual immunotherapy for hazelnut food allergy: a follow-up study. *Ann Allergy asthma Immunol* 2008;100:283–4.
56. Fernandez-Rivas M, Garrido Fernandez S, Nadal JA, et al. Randomized double-blind, placebo-controlled trial of sublingual immunotherapy with a Pru p 3 quantified peach extract. *Allergy* 2009;64:876–83.

57. Kim EH, Bird JA, Kulis M, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. *J Allergy Clin Immunol* 2011; 127:640–6.e1.
58. 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;135:1240–8.e1-3.
59. 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;131:119–27.e1-7.
60. Pautrizel R, Cabanieu G, Bricaud H, et al. Allergenic group specificity & therapeutic consequences in asthma; specific desensitization method by epicutaneous route. *Sem Hop* 1957;33:1394–403 [in French].
61. Dioszeghy V, Mondoulet L, Dhelft V, et al. Epicutaneous immunotherapy results in rapid allergen uptake by dendritic cells through intact skin and downregulates the allergen-specific response in sensitized mice. *J Immunol* 2011;186:5629–37.
62. 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;125:1165–7.
63. 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* 2016;139(4):1242–52.e9.