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Next-Generation Approaches for the Treatment of Food Allergy

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Abstract

Purpose of Review IgE-mediated food allergies are an increasing health concern, and current management includes food avoidance and use of emergency medications. Effective treatment of food allergy is highly desirable. Next generation approaches for the treatment of food allergy aim to improve both safety and efficacy, potentially including long-term tolerance.

Recent Findings Oral immunotherapy (OIT) and epicutaneous immunotherapy (EPIT) will likely be integrated into clinical practice as part of food allergy management in the near future. Newer approaches, such as sublingual immunotherapy (SLIT), modified proteins, lysosomal-associated membrane protein DNA (LAMP DNA) vaccines, and the use of immunomodulatory agents, are early in development and depending on results, could also become important treatment options.

Summary This is a review of novel approaches to the treatment of food allergy that are currently under investigation, including the use of SLIT, modified proteins, probiotics, Chinese herbal supplements, biologic therapies, and DNA vaccines, as well as a summary of the current status of OIT and EPIT.

Keywords Food allergy · Treatment · Immunotherapy · Biologic therapy · Modified proteins · DNA vaccine

Introduction

IgE-mediated food allergies are an increasing health concern and are reported to affect 6 to 8% of children and 1–2% of adults in the USA [1–4]. Allergies to peanut, tree nuts, and shellfish have low rates of resolution, and a substantial proportion of milk and egg allergy will persist into adolescence and adulthood [5]. To date, standard management is food avoidance and use of emergency medications as needed [1]. Rates of adverse reactions vary but can be severe and have been shown to occur frequently and to a variety of food products [6–10]. Furthermore, food allergy has been shown to negatively impact quality of life and nutrition [11–14]. For all these reasons, effective treatment of food allergy is highly desirable.

Research on potential treatments for food allergy is a rapidly expanding field, and it is highly likely that there will be an FDA-approved product for the treatment of peanut allergy within the next few years. Clinical trials have primarily focused on the use of allergen-specific immunotherapy (AIT), which utilizes exposure to an allergen in gradually increasing doses with the goal of inducing desensitization and possibly tolerance. Oral (OIT), epicutaneous (EPIT), sublingual (SLIT), and subcutaneous (SCIT) routes of AIT are currently under investigation. Currently, these approaches remain experimental; however, OIT and EPIT for peanut allergy have completed phase III trials (NCT03211247, NCT02635776). Next-generation approaches aim to improve both safety and efficacy, potentially including long-term tolerance. Here, we review novel approaches to the treatment of food allergy that are currently under investigation, including the use of SLIT, modified proteins, probiotics, Chinese herbal supplements, biologic therapies, and DNA vaccines, as well as a summary of the current status of OIT and EPIT (Table 1).

Oral Immunotherapy

Oral immunotherapy (OIT) involves ingestion of an allergen that is typically mixed in some food vehicle and then ingested daily. Protocols differ, but most OIT trials use a maintenance dose of 300 to 4000 mg of food protein daily [15, 16]. Numerous foods have been studied, but the majority of studies

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Table 1 Novel approaches to food allergy treatment

Therapy	Immunologic mechanism	Benefits	Limitations	Additional comments
Oral immunotherapy	Antigen presentation to mucosal sites can lead to desensitization and possibly tolerance. Associated with changes in Th2 phenotype	Most patients who tolerate therapy can be successfully desensitized. Possible sustained unresponsiveness (SU)	Immunologic changes may be temporary. High rate of adverse reactions.	Studied as single and multi-food monotherapy and in combination with various adjuvants AR101 for peanut allergy granted FDA Breakthrough Therapy Designation status.
Sublingual immunotherapy		Well tolerated. Can lead to modest desensitization	Lesser effect than OIT for efficacy and immune response. Effect on tolerance/SU is unclear.	Studied in peanut, milk, hazelnut, and fruits
Epicutaneous immunotherapy	Antigen presented through the skin is taken up by dendritic cells and can lead to desensitization. Associated with changes in Th2 phenotype	Shown to increase reaction threshold Best safety profile compared to OIT or SLIT.	More modest effect than OIT or SLIT No data on SU	Studied for peanut and milk. Viaskin patch peanut allergy granted FDA Breakthrough Therapy Designation status and submitted to the FDA for drug approval in October 2018.
Anti-IgE	Binds to the C_H3 domain of the free IgE molecule and prevents IgE from binding to effector cells and cross-linking.	Shown to increase dose threshold. Used in combination with OIT, can decrease time required to reach maintenance and adverse events	Dosing limitations based on weight, IgE, and age.	Limited number of clinical trials Being investigated as monotherapy and in combination with OIT. Not food-specific
Modified proteins	Allergenic proteins are altered in a way to still induce desensitization, but lower risk of IgE-mediated reaction.	Possibly safer than immunotherapy with native protein	Limited studies	Currently under investigation: -HAL-MPE1 peanut extract -mCYP for fish allergy -PVX108—synthetic peptides for peanut allergy
DNA vaccine	Induction of Th1 cellular and humoral responses in murine models	Phase 1 trial underway	Appeared to be safe in murine models	ASP0892 is in phase 1 trials for the treatment of peanut allergy
Chinese herbal supplements	In murine models, led to decreased Th2 response with allergen exposure and decreased mast cell degranulation and histamine release	Murine models showed that FAHF-2 prevented food-induced anaphylaxis and that OIT plus FAHF-2 decreased number of adverse events. Human studies have not shown efficacy	Limited studies. Appears to be safe	FAHF-2 is a combination of nine Chinese herbs that has been used as monotherapy and with OIT
Adjuncts to OIT	Varies based on adjunct	Goal of reducing side effects and improving efficacy	Limited studies	-CpG-coated polynanoparticles plus peanut OIT - FAHF-2 - Biologics - probiotics

have focused on single-allergen OIT with milk, egg, or peanut [17–25, 26•, 27••]. OIT trials have shown that most patients who tolerate therapy can be successfully desensitized, but longer term tolerance or sustained unresponsiveness (SU) appears to be uncommon [28, 29••]. Safety remains a major concern with OIT given that it is associated with high rates of adverse reactions [15, 28]. Most reactions are mild with abdominal pain being the most common symptom. However, more severe reactions can occur. More severe reactions are more common during buildup, but they can occur at any time point and most concerning, many are unpredictable and occur to a previously tolerated dose [15, 28]. In addition, about 10–20% of patients drop out of OIT trials with the most common complaint being chronic abdominal pain [15]. Furthermore, eosinophilic esophagitis has been documented, although the true incidence of OIT-triggered eosinophilic esophagitis remains unknown [15, 30, 31].

AR101 is a novel drug powder that is being investigated in OIT studies for the treatment of peanut allergy in children and adolescents. In September 2014, AR101 received the U. S Food and Drug administration (FDA) Fast Track Designation. Results of the phase 2 trial of AR101 were

published in March 2018 [27••]. Seventy-nine percent of the AR101 group compared to 19% of the placebo group tolerated ≥ 443 mg of peanut protein at exit double-blind placebo-controlled food challenge (DBPCFC) with no or mild symptoms ($p < 0.0001$) [27••]. In June 2018, the FDA granted Breakthrough Therapy Designation Status to AR101. Phase 3 trials of AR101 were recently completed (NCT02635776, NCT03126227) and a third is underway in Europe (NCT03201003).

Newer approaches have investigated OIT combined with an adjuvant or an immunomodulatory agent [32–36]. In 2016, Srivastava et al. published a preclinical, mouse model study of peanut OIT using CpG-coated polynanoparticles (CgG/PN-NPs) [36]. The investigators found that mice with peanut allergy treated with CpG/PN-NPs were significantly protected from anaphylaxis during oral peanut challenges, compared to untreated control mice [36]. The authors conclude the peanut OIT with CpG/PN-NPs might be useful approach in humans.

FA herbal formula-2 (FAHF-2) is a combination of nine Chinese herbs that has been explored as monotherapy and in combination with OIT as a treatment for food allergy. Murine models demonstrated that FAHF-2 prevented peanut-, egg-, and fish-induced anaphylaxis [37, 38]. Another pre-clinical trial combined peanut, walnut, or cashew OIT with the Chinese herbal formula B-FAHF-2 and found that OIT + B-FAHF-2 mice had significantly fewer and less severe adverse reactions than mice treated with OIT alone [39]. In 2015, Wang et al. published the results of a phase 1 study that evaluated the safety and effectiveness of FAHF-2 as treatment for peanut, tree nut, sesame, fish, and/or shellfish allergy. After 6 months of treatment, FAHF-2 appeared to be safe, but did not appear to increase tolerance to a food [40]. Currently, a phase 2 study of E-B-FAHF-2 plus multi-food OIT and omalizumab is underway with estimated study completion in 2021 (NCT02879006).

The co-administration of probiotics with OIT has been investigated as a newer treatment option for food allergy. Tang et al. performed a double-blind, placebo-controlled trial of *Lactobacillus rhamnosus* CGMCC and peanut OIT (PPOIT) in children with peanut allergy [34]. The primary outcome was sustained unresponsiveness 2 to 5 weeks after stopping treatment. 82.1% in the PPOIT group compared to 3.6% receiving placebo had possible sustained unresponsiveness. The group found that PPOIT was associated with an improvement in food allergy quality of life at 3 and 12 months post-treatment with improvement in scores related to achievement of sustained unresponsiveness [41].

Omalizumab is a recombinant, monoclonal antibody that selectively binds to human IgE [42]. It has been explored as both pre-treatment and in conjunction with OIT for the treatment of milk, egg, peanut, and multi-food allergies [43, 44•, 45–47]. Studies have shown that omalizumab decreases adverse events and can significantly decrease the time required to reach maintenance dosing [33]. As noted earlier, a phase 2 study of Chinese herbs, multi-food OIT, and omalizumab is underway (NCT02879006).

Epicutaneous Immunotherapy

Epicutaneous immunotherapy (EPIT) involves delivering allergen via a small patch that is applied to the skin and then changed approximately every 24 h [16, 48••, 49, 50]. Typically, protocols start with patch application for a few hours a day with a gradual increase to 24 h per day [51]. The patch applied can contain 50–500 μg of food protein. EPIT has been investigated for the treatment of peanut and milk allergy [48••, 49, 50]. EPIT has been shown to increase reaction threshold, with the greatest effect seen in younger children, but with a more modest effect than OIT or SLIT [50, 51]. To date, EPIT has been very well tolerated with most adverse events limited to local erythema or eczema at the patch application site [49, 50]. EPIT has the best safety profile compared to OIT or SLIT [51].

Viaskin is a peanut patch that received FDA Fast Track Designation in 2012 and granted Breakthrough Therapy Designation Status in 2015. The phase 2 study compared 2 doses of Viaskin peanut (VP100 and VP250) to placebo in children and young adults [48••]. The primary end point was the proportion of participants who after 52 weeks passed a DBPCFC with 5044 mg of peanut protein or had a ≥ 10-fold increase in the successfully consumed dose of peanut protein compared with the baseline oral food challenge (OFC). The primary end point was met in 12% of the placebo group, 45.8% of the VP100 group, and 48% of the VP250 group. The effect of treatment was greater in the younger age group with little or no improvement in those over 11 years. A second phase 2 trial demonstrated similar results except that the 100 mcg dose was no longer superior to placebo [52]. There is an ongoing, open-label, follow-up study of subjects who participated in earlier peanut patch study with the goal to evaluate the safety and long-term efficacy of the product (NCT03013517). EPITOPE is an ongoing study of the safety and efficacy of Viaskin peanut patch in 1- to 3-year-old children (NCT03211247).

The company has announced preliminary results of phase 3 trials that showed a 35.3% response rate in those on Viaskin peanut 250 μg for 12 months compared to 13.6% of patients in the placebo arm. However, the study's statistical analysis plan (SAP) submitted to the FDA proposed a 15% difference in the 95% confidence interval response rates between the active and placebo arms, and the study did not reach the 15% lower bound of the confidence interval. Nonetheless, in October 2018, the company applied for FDA license for Viaskin peanut patch therapy.

Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) involves placing a liquid extract with the food allergen sublingually for 2–3 min and then swallowing daily. Typical maintenance doses are 1 to 10 mg and limited by extract concentration and volume [15]. SLIT studies have focused predominately on peanut, milk, hazelnut, and fresh fruits [53–60]. SLIT has been shown to provide moderate desensitization, defined in most studies as an increase in oral food challenge threshold, without long-term SU [15, 16]. Studies have shown that SLIT is well tolerated, with adverse reactions mainly limited to itching and tingling of the oropharynx and few systemic side effects [29••].

In 2011, Kim et al. published the first double-blind placebo-controlled (DBPC) trial of SLIT for the treatment of peanut allergy [55]. During this trial, 18 children (1–11 years) completed 6 months of SLIT dose escalation and 6 months of maintenance dosing and then a DBPC peanut OFC. The treatment group tolerated 20 times more peanut protein (median, 1710 mg) than the placebo group (median, 85 mg), $p = 0.11$. Investigators also noted immunologic changes with peanut SLIT.

A larger, DBPC peanut SLIT study of 40 subjects, age 12–37 years, was published in 2013 by Fleischer et al. [56]. During phase 1, subjects who had a 2-g baseline peanut OFC were randomized to peanut or placebo SLIT for 44 weeks and then competed a 5-g peanut powder (2.5 g peanut protein) OFC. The second phase of the study was an unblinded additional 120 weeks of lower-dose peanut SLIT for the initial active treatment group and 164 weeks of higher-dose peanut SLIT for the placebo subjects who crossed over to active. Three subjects withdrew (2 peanut, 1 placebo). A responder was defined as one who could consume without dose-limiting symptoms a (1) cumulative dose of 5 g of peanut powder at the week-44 OFC or a (2) 10-fold increase in the amount of peanut powder tolerated at week 44 compared to baseline. Seventy percent of the peanut SLIT group compared to 15% of the placebo group was responders after 44 weeks of SLIT. The median successfully consumed dose-increased in the peanut-SLIT responders from 3.5 to 496 mg. This median dose further increased after 68 weeks of SLIT to 996 mg. Overall, SLIT was well tolerated with the most common symptoms being oral/pharyngeal.

A 3-year, long-term study from this trial showed 98% of doses were tolerated without adverse reactions; however > 50% of subjects discontinued therapy [57]. After 3 years of treatment with SLIT, treatment was stopped for 8 weeks and then a 10-g OFC and open feeding of peanut butter were completed. At the end of the study, 4/37 (10.8%) of SLIT-treated subjects tolerated 10 g of peanut powder and those 4 had sustained unresponsiveness [57].

SAR439794 is a peanut extract with glucopyranosyl lipid A (GLA) that is currently in phase 1 trials for the treatment of peanut allergy (NCT0343135).

In a more recent study published in 2018, Kinaciyan et al. evaluated the use of recombinant birch pollen allergen (rBet v1) SLIT or recombinant major apple allergen (rMal d1) SLIT to treat birch pollen–related apple allergy [60]. Only SLIT with rMal d1 significantly improved apple allergy. Both extracts appeared to be safe.

There have been limited studies comparing SLIT and OIT. Narisety et al. completed a randomized, DBPC pilot study of SLIT compared to OIT for the treatment of peanut allergy [53]. Twenty-one subjects age 7–13 years were randomized and 16/21 discontinued therapy during the first year. The investigators found that all 16 subjects had a > 10-fold increase in challenge threshold after 12 months of OIT or SLIT, but that the increase in dose was significantly greater in the active OIT group (141-fold vs 22-fold, $p = 0.01$). Reactions were more common in the OIT group.

Keet et al. compared the safety and efficacy of SLIT alone compared to SLIT followed by OIT for the treatment of milk allergy [54]. Thirty children age 6 to 17 years were enrolled. More subjects in the SLIT/OIT group passed the 8-g end-of-treatment challenge compared to the SLIT-alone group (6/10 vs 1/10, $p = 0.002$). Overall reaction rates were similar between groups; however, systemic reactions were more common during OIT.

Biologics

Over the past several years, multiple biologics have been approved for the treatment of allergic diseases and many others are currently in development [61]. Omalizumab is approved for the treatment of allergic asthma and chronic idiopathic urticaria, and over the past decade, it has been explored as a potential treatment for food allergy. In addition to its use as an adjunct to OIT, omalizumab and its analog TNX-901 have been shown to have potential as a monotherapy treatment for food allergy [62, 63]. In the study of TNX-901 by Leung et al., a dose-related effect on peanut challenge was demonstrated, with the highest dose (450 mg) leading to an increase in the threshold dose from 178 to 2805 mg of peanut flour [62]. Savage et al. studied the effects of omalizumab in peanut allergic adults and found a significant and rapid effect, with the median cumulative threshold dose of peanut protein increasing from 80 mg at baseline to 6500 mg at weeks 4–8 [64]. Of further note in this regard, Genentech recently announced that the U.S. Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation for omalizumab for the prevention of severe allergic reactions following accidental exposure to one or more foods in people with allergies. An additional line of evidence supporting the effect of

omalizumab on acute food-allergic reactions emerges from the many studies demonstrating the ability to rapidly increase OIT doses under the protection of omalizumab [43, 44•, 45–47].

IL-33 is a member of the IL-1 cytokine family, and mouse models have shown that IL-33 appears to be necessary for inducing IgE-dependent anaphylaxis in the gut [65]. ANB020 is a monoclonal anti-IL 33 antibody that is under investigation for the treatment of peanut allergy. A phase 1 study of ANB020 in healthy volunteers showed that ANB020 was well tolerated and the pharmacokinetic profiles were explored for intravenous and subcutaneous regimens [66]. A phase 2, multi-center, randomized, double-blind, placebo-controlled proof-of-concept study on the safety and efficacy of ANB020 in peanut allergic adults was recently completed in March 2018 (NCT02920021). To date, results have not been published.

Dupilumab is a monoclonal antibody that targets IL-4 receptor alpha that is approved for the treatment of asthma and atopic dermatitis. A phase 2 trial is planned to evaluate the efficacy and safety of dupilumab as adjunct to AR101 peanut oral immunotherapy (NCT03682770).

Modified Proteins

As an attempt to improve the safety of food allergy immunotherapy, a newer approach is to use modified allergenic proteins that have been altered so that they can still induce desensitization, but with a lower risk of IgE-mediated reactions. In 2013, a phase 1 trial explored the use of EMP-123, a vaccine consisting of 3 recombinant peanut antigens (Ara h1, Ara h2, Ara h3), encapsulated within heat/phenol inactivated *E. coli* (NCT00850668) [67]. Healthy ($n = 5$) and then peanut allergic ($n = 10$) patients were given weekly, escalating doses as a rectal suspension. Investigators found that adverse reactions were common in peanut allergic subjects and 5/10 (50%) could not complete dosing and 2/10 (20%) had severe allergic reactions. The authors concluded that this product would require changes in route of administration and/or dosing scheme in future studies.

Subcutaneous immunotherapy (SCIT) delivers allergen by subcutaneous injections given under clinical supervision. HAL-MPE1 is a chemically modified, aluminum hydroxide–adsorbed peanut extract for subcutaneous administration. In 2015, a first-in-human, randomized, double-blind, placebo-controlled trial in Denmark established the safety of HAL-MPE1 in 17 peanut allergic adults (NCT02163018). Patients were randomized to receive 4–5 months of increasing doses of HAL-MPE1 ($n = 11$) or placebo ($n = 6$). Preliminary results showed HAL-MPE1 was generally well tolerated [68]. A phase 1 randomized, double-blind, placebo-controlled, multi-center study is currently underway in the USA and Canada (NCT02991885). The aim of this study is to assess the safety and tolerability of HAL-MPE1 SCIT in peanut allergic adults, and then adolescents and children.

Zuidmeer-Jongejan et al. selected a mutant CYP (mCYP) c1 to create an alum-adsorbed, hypoallergenic parvalbumin vaccine for SCIT in those with fish allergy [69]. Preclinical trials showed that mCyp c1 had significantly reduced allergenic activity with an average 1000-fold reduction compared to recombinant Cyp (rCyp). These results led to a phase 1 study of the recombinant mCyp c1 vaccine (FAST-Fish-Food Allergy Specific Treatment for Food Allergy), which was completed in October 2014 (NCT02017626), and the FASTIIb trial was a phase IIb clinical trial using recombinant hypoallergenic parvalbumin (mCyp c1), which was completed in April 2017 (NCT02382718). As of the time of this publication, results were not published for either study.

PVX108 is a product composed of synthetic peptides representing T cell epitope sequences from Ara h1 and Ara h2 [70]. PVX108 is administered by intradermal injection with the goal that it will induce tolerance to peanut without the risk of immediate allergic reactions. A two-stage first-in-human trial is now underway in Australia (Australian New Zealand Clinical Trials Registry #ACTRN12617000692336) during which investigators will assess the safety of a single dose of PVX108 (stage 1) and then up to 6 escalating doses given every 2 weeks for up to 16 weeks (stage 2) in peanut allergic individuals.

DNA Vaccine

Another new approach to the treatment of peanut allergy is use of a DNA vaccine. ASP0892 (ARA LAMP Vax) is single multivalent peanut (Ara h1, h2, h3) lysosomal-associated membrane protein (LAMP) DNA plasmid vaccine. Su et al. designed a LMP DNA vaccine for Japanese Red Cedar allergy and showed the CryJ-LAMP vaccine seemed to induce aTh1 response in mice [71]. The phase 1 trial indicated that the CryJ2-LAMP DNA vaccine is safe [72]. A phase 1 randomized, placebo-controlled trial is currently evaluating the safety and tolerability of ASP0892 after intramuscular or intradermal injection in adults with peanut allergy (NCT02851277). Participants receive (1) low-dose ASP0892 intradermal, (2) high-dose ASP0892 intradermal, (3) placebo intradermal, (4) high-dose ASP0892 intramuscular, or (5) placebo intramuscular. All groups receive an injection once every 2 weeks for a total of 4 doses.

Conclusions

Research on potential treatments for food allergy is a rapidly expanding field and multiple trials are currently underway. To date, these treatments have had variable levels of success, but

none have led to a cure. Compared to EPIT and SLIT, OIT has shown the most promising regarding the efficacy and the ability to increase the eliciting dose threshold; however, OIT also has a higher rate of adverse events [28, 53, 54, 73]. Peanut OIT and EPIT products have now been submitted for FDA licensing. The Food and Drug Administration has designated AR101 peanut OIT therapy and Viaskin peanut patch as a "breakthrough therapy," which will accelerate the development and review of this treatment. OIT and EPIT will likely be integrated into clinical practice as part of food allergy management in the near future. The use of biologics is also under investigation, and omalizumab has been granted Breakthrough Therapy Designation for the prevention of severe allergic reactions following accidental exposure to one or more foods in people with allergies. Newer approaches, such as SLIT, modified proteins, LAMP DNA vaccines, and the use of immunomodulatory agents, are early in development and depending on results, could also become important treatment options.

Compliance with Ethical Standards

Conflict of Interest Dr. Dantzer reports grants from NIH, grants from Aimmune, and personal fees from Maryland Chapter of the American Academy of Pediatrics, outside the submitted work; Dr. Wood reports grants from NIH, from Aimmune, from Astellas, from DBV, from Sanofi, from regeneron, and other from Up To Date, outside the submitted work.

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References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. Nutr Res. 2011;31(1):61–75.
2. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics. 2011;128(1):e9–17.
3. Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol. 2011;127(3):594–602.
4. Prescott SL, Pawankar R, Allen KJ, Campbell DE, Sinn JK, Fiocchi A, et al. A global survey of changing patterns of food allergy burden in children. World Allergy Organ J. 2013;6(1):21-4551-6-21.
5. Savage J, Sicherer S, Wood R. The natural history of food allergy. J Allergy Clin Immunol Pract. 2016;4(2):196–203 quiz 204.
6. Blom WM, Michelsen-Huisman AD, van Os-Medendorp H, van Duijn G, de Zeeuw-Brouwer ML, Versluis A, et al. Accidental food allergy reactions: products and undeclared ingredients. J Allergy Clin Immunol. 2018;142(3):865–75.
7. Versluis A, Knulst AC, Kruizinga AG, Michelsen A, Houben GF, Baumert JL, et al. Frequency, severity and causes of unexpected allergic reactions to food: a systematic literature review. Clin Exp Allergy. 2015;45(2):347–67.
8. Nguyen-Luu NU, Ben-Shoshan M, Alizadehfar R, Joseph L, Harada L, Allen M, et al. Inadvertent exposures in children with peanut allergy. Pediatr Allergy Immunol. 2012;23(2):133–9.
9. Fleischer DM, Perry TT, Atkins D, Wood RA, Burks AW, Jones SM, et al. Allergic reactions to foods in preschool-aged children in a prospective observational food allergy study. Pediatrics. 2012;130(1):e25–32.
10. Michelsen-Huisman AD, van Os-Medendorp H, Blom WM, Versluis A, Castenmiller JJM, Noteborn HPJM, et al. Accidental allergic reactions in food allergy: causes related to products and patient's management. Allergy. 2018; 73(12):2377-2381.
11. Kim J, Kwon J, Noh G, Lee SS. The effects of elimination diet on nutritional status in subjects with atopic dermatitis. Nutr Res Pract. 2013;7(6):488–94.
12. Hobbs CB, Skinner AC, Burks AW, Vickery BP. Food allergies affect growth in children. J Allergy Clin Immunol Pract. 2015;3(1):133–4.e1.
13. Cummings AJ, Knibb RC, King RM, Lucas JS. The psychosocial impact of food allergy and food hypersensitivity in children, adolescents and their families: a review. Allergy. 2010;65(8):933–45.
14. Flokstra-de Blok BM, Dubois AE, Vlieg-Boerstra BJ, Oude Elberink JN, Raat H, DunnGalvin A, et al. Health-related quality of life of food allergic patients: comparison with the general population and other diseases. Allergy. 2010;65(2):238–44.
15. Wood RA. Oral immunotherapy for food allergy. J Investig Allergol Clin Immunol. 2017;27(3):151–9.
16. Burks AW, Sampson HA, Plaut M, Lack G, Akdis CA. Treatment for food allergy. J Allergy Clin Immunol. 2018;141(1):1–9.
17. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008;122(6):1154–60.
18. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008;121(2):343–7.
19. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol. 2010;105(5):376–81.
20. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. J Allergy Clin Immunol. 2007;119(1):199–205.
21. Vickery BP, Pons L, Kulis M, Steele P, Jones SM, Burks AW. Individualized IgE-based dosing of egg oral immunotherapy and the development of tolerance. Ann Allergy Asthma Immunol. 2010;105(6):444–50.
22. Jones SM, Burks AW, Keet C, Vickery BP, Scurlock AM, Wood RA, et al. Long-term treatment with egg oral immunotherapy enhances sustained unresponsiveness that persists after cessation of therapy. J Allergy Clin Immunol. 2016;137(4):1117–1127.e10.
23. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, 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(9925):1297–304.

24. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol. 2010;126(1):83–91.e1.
25. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol. 2011;127(3):654–60.
26.• Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017;139(1):173–181.e8 **Study showing the safety and efficacy of peanut OIT in young children.**
27.•• Bird JA, Spergel JM, Jones SM, Rachid R, Assa'ad AH, Wang J, et al. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of ARC001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. J Allergy Clin Immunol Pract. 2018;6(2):476–485.e3 **Phase 2 results from AR101 product that will be submitted to the FDA for new drug licensing.**
28. Wood RA. Food allergen immunotherapy: current status and prospects for the future. J Allergy Clin Immunol. 2016;137(4):973–82.
29.•• Scurlock AM, Jones SM. Advances in the approach to the patient with food allergy. J Allergy Clin Immunol. 2018;141(6):2002–14 **Excellent overview of diagnosis, management, and treatment approaches to food allergy.**
30. Sanchez-Garcia S, Rodriguez Del Rio P, Escudero C, Martinez-Gomez MJ, Ibanez MD. Possible eosinophilic esophagitis induced by milk oral immunotherapy. J Allergy Clin Immunol. 2012;129(4):1155–7.
31. Ridolo E, De Angelis GL, Dall'aglio P. Eosinophilic esophagitis after specific oral tolerance induction for egg protein. Ann Allergy Asthma Immunol. 2011;106(1):73–4.
32. Begin P, Winterroth LC, Dominguez T, Wilson SP, Bacal L, Mehrotra A, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. Allergy Asthma Clin Immunol. 2014;10(1):1-1492-10-1.
33. Dantzer JA, Wood RA. The use of omalizumab in allergen immunotherapy. Clin Exp Allergy. 2018 Mar;48(3):232–40.
34. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: a randomized trial. J Allergy Clin Immunol. 2015;135(3):737–44.e8.
35. Goldberg MR, Nachshon L, Appel MY, Elizur A, Levy MB, Eisenberg E, et al. Efficacy of baked milk oral immunotherapy in bakedmilk-reactive allergic patients. J Allergy Clin Immunol. 2015;136(6):1601-1606.
36. Srivastava KD, Siefert A, Fahmy TM, Caplan MJ, Li XM, Sampson HA. Investigation of peanut oral immunotherapy with CpG/peanut nanoparticles in a murine model of peanut allergy. J Allergy Clin Immunol. 2016;138(2):536–543.e4.
37. Srivastava KD, Bardina L, Sampson HA, Li XM. Efficacy and immunological actions of FAHF-2 in a murine model of multiple food allergies. Ann Allergy Asthma Immunol. 2012;108(5):351–358.e1.
38. Srivastava KD, Kattan JD, Zou ZM, Li JH, Zhang L, Wallenstein S, et al. The Chinese herbal medicine formula FAHF-2 completely blocks anaphylactic reactions in a murine model of peanut allergy. J Allergy Clin Immunol. 2005;115(1):171–8.
39. Srivastava KD, Song Y, Yang N, Liu C, Goldberg IE, Nowak-Wegrzyn A, et al. B-FAHF-2 plus oral immunotherapy (OIT) is safer and more effective than OIT alone in a murine model of concurrent peanut/tree nut allergy. Clin Exp Allergy. 2017;47(8):1038–49.
40. Wang J, Jones SM, Pongracic JA, Song Y, Yang N, Sicherer SH, et al. Safety, clinical, and immunologic efficacy of a Chinese herbal medicine (food allergy herbal formula-2) for food allergy. J Allergy Clin Immunol. 2015;136(4):962–970.e1.
41. Dunn Galvin A, McMahon S, Ponsonby AL, Hsiao KC, Tang MLK. PPOIT study team. The longitudinal impact of probiotic and peanut oral immunotherapy on health-related quality of life. Allergy. 2018;73(3):560–8.
42. Xolair(R) [package insert]. Genentech, Inc., South San Francisco, CA, 2007. 2017; Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2007/103976s5102lbl.pdf. Accessed September 12, 2017.
43. Andorf S, Purington N, Block WM, Long AJ, Tupa D, Brittain E, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. Lancet Gastroenterol Hepatol. 2018;3(2):85–94.
44.• Wood RA, Kim JS, Lindblad R, Nadeau K, Henning AK, Dawson P, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol. 2016;137(4):1103–10.e1–11 **Study showing that omalizumab plus OIT improved safety, but not efficacy.**
45. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol. 2017;139(3):873–881.e8.
46. Nadeau KC, Schneider LC, Hoyte L, Borras I, Umetsu DT. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol. 2011 Jun;127(6):1622–4.
47. Lin C, Lee IT, Sampath V, Dinakar C,DeKruyff RH, Schneider LC, et al. Combining anti-IgEwith oral immunotherapy. Pediatr Allergy Immunol. 2017; 28(7): 619-627.
48.•• Jones SM, Sicherer SH, Burks AW, Leung DY, Lindblad RW, Dawson P, et al. Epicutaneous immunotherapy for the treatment of peanut allergy in children and young adults. J Allergy Clin Immunol. 2017;139(4):1242–1252.e9 **Phase II results on the safety and efficacy of Viaskin peanut patch therapy, which was submitted to the FDA for licensing in October 2018.**
49. Dupont C, Kalach N, Soulaines P, Legoue-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol. 2010 May;125(5):1165–7.
50. Jones SM, Agbotounou WK, Fleischer DM, Burks AW, Pesek RD, Harris MW, et al. Safety of epicutaneous immunotherapy for the treatment of peanut allergy: a phase 1 study using the Viaskin patch. J Allergy Clin Immunol. 2016;137(4):1258–1261.e10.
51. Feuille E, Nowak-Wegrzyn A. Allergen-specific immunotherapies for food allergy. Allergy Asthma Immunol Res. 2018;10(3):189–206.
52. Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, 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(18):1798–809.
53. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol. 2015;135(5):1275–82.e1–6.
54. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012;129(2):448–55 455.e1–5.
55. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011;127(3):640–6.e1.

56. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131(1):119–27.e1–7.
57. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, et al. Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol. 2015;135(5):1240–8.e1–3.
58. de Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. Allergy. 2006;61(10): 1238–9.
59. Enrique E, Pineda F, Malek T, Bartra J, Basagana M, Tella R, et al. Sublingual immunotherapy for hazelnut food allergy: a randomized, double-blind, placebo-controlled study with a standardized hazelnut extract. J Allergy Clin Immunol. 2005;116(5):1073–9.
60. Kinaciyan T, Nagl B, Faustmann S, Frommlet F, Kopp S, Wolkersdorfer M, et al. Efficacy and safety of 4 months of sublingual immunotherapy with recombinant Mal d 1 and Bet v 1 in patients with birch pollen-related apple allergy. J Allergy Clin Immunol. 2018;141(3):1002–8.
61. Manka LA, Wechsler ME. New biologics for allergic diseases. Expert Rev Clin Immunol. 2018;14(4):285–96.
62. Leung DY, Sampson HA, Yunginger JW, Burks AW Jr, Schneider LC, Wortel CH, et al. Effect of anti-IgE therapy in patients with peanut allergy. N Engl J Med. 2003;348(11):986–93.
63. Sampson HA, Leung DY, Burks AW, Lack G, Bahna SL, Jones SM, et al. A phase II, randomized, double-blind, parallel-group, placebo-controlled oral food challenge trial of Xolair (omalizumab) in peanut allergy. J Allergy Clin Immunol. 2011;127(5):1309–10.e1.
64. Savage JH, Courneya JP, Sterba PM, Macglashan DW, Saini SS, Wood RA. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. J Allergy Clin Immunol. 2012;130(5):1123–1129.e2.
65. Muto T, Fukuoka A, Kabashima K, Ziegler SF, Nakanishi K, Matsushita K, et al. The role of basophils and proallergic cytokines, TSLP and IL-33, in cutaneously sensitized food allergy. Int Immunol. 2014;26(10):539–49.
66. Marco Londei M, Brian Kenney B, Gerrit Los P, Margaret MP. A phase 1 study of ANB020, an anti-IL-33 monoclonal antibody, in healthy volunteers. J Am Acad Dermatol. 2017; 2018/11;76(6): AB20.
67. Wood RA, Sicherer SH, Burks AW, Grishin A, Henning AK, Lindblad R, et al. A phase 1 study of heat/phenol-killed, *E. coli*-encapsulated, recombinant modified peanut proteins Ara h 1, Ara h 2, and Ara h 3 (EMP-123) for the treatment of peanut allergy. Allergy. 2013;68(6):803–8.
68. Bindslev-Jensen C, de Kam P, van Twuijver E, Boot DB, El Galta R, Mose AP, et al. SCIT-treatment with a chemically modified, aluminum hydroxide adsorbed peanut extract (HAL-MPE1) was generally safe and well tolerated and showed immunological changes in peanut allergic patients. J Allergy Clin Immunol. 2017; 2018/10;139(2):AB191.
69. Zuidmeer-Jongejan L, Huber H, Swoboda I, Rigby N, Versteeg SA, Jensen BM, et al. Development of a hypoallergenic recombinant parvalbumin for first-in-man subcutaneous immunotherapy of fish allergy. Int Arch Allergy Immunol. 2015;166(1):41–51.
70. Prickett SR, Voskamp AL, Phan T, Dacumos-Hill A, Mannering SI, Rolland JM, et al. Ara h 1 CD4+ T cell epitope-based peptides: candidates for a peanut allergy therapeutic. Clin Exp Allergy. 2013;43(6):684–97.
71. Su Y, Connolly M, Marketon A, Heiland T. CryJ-LAMP DNA vaccines for Japanese Red Cedar allergy induce robust Th1-type immune responses in murine model. J Immunol Res. 2016;2016: 4857869.
72. Su Y, Romeu-Bonilla E, Anagnostou A, Fitz-Patrick D, Hearl W, Heiland T. Safety and long-term immunological effects of CryJ2-LAMP plasmid vaccine in Japanese red cedar atopic subjects: a phase I study. Hum Vaccin Immunother. 2017;13(12):2804–13.
73. Chin SJ, Vickery BP, Kulis MD, Kim EH, Varshney P, Steele P, et al. Sublingual versus oral immunotherapy for peanut-allergic children: a retrospective comparison. J Allergy Clin Immunol. 2013;132(2):476–8.e2.