REPORT

Management of Peanut Allergy: A Focus on Novel Immunotherapies

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ABSTRACT

The management of peanut allergy involves strict avoidance, prompt recognition of allergic reactions, and rapid initiation of epinephrine and other supportive therapy for anaphylaxis. Avoidance presents several challenges and burdens to quality of life and daily activities. Currently, no treatment options are available for peanut allergy apart from epinephrine, which is the treatment of choice for severe allergic reactions. In recognition of the need for improved treatment options among patients with peanut allergy, several novel immunotherapies are undergoing clinical development, and clinicians must be knowledgeable about the safety and efficacy of these agents. This educational activity will provide an overview of current practices in peanut allergy management and novel immunotherapies with potential to improve outcomes among children and adults with peanut allergy.

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For author information and disclosures, see end of text.

Because even a small amount of allergen can induce a systemic reaction in an individual with peanut allergy, strict avoidance is necessary to prevent life-threatening complications.[1] However, effective avoidance presents several challenges to patients and their families, leading to substantial burdens to quality of life and daily activities.[2,3] For example, Avery et al found that children with peanut allergy felt more threatened by potential hazards within their environment, more restricted regarding physical activity, and more worried about being away from home than did children with insulin-dependent diabetes.[2] Alongside children's burdens, parents also report significant disruption of daily activities due to avoidance measures.[4,5] When dining out, adults with peanut allergy have reported social embarrassment from the need to check whether a particular food contains peanuts, and wanting to avoid this embarrassment can lead to increased risk-taking behaviors.[3] Additionally, the need to seek familiarity in choice of establishment to reduce anxiety led to a lack of spontaneity in daily living, which was a regret for some adults with peanut allergy.[3] While traveling, research has shown that peanut exposures can and do commonly occur on commercial airline flights, leaving many individuals with the responsibility of cleaning their own seats and not consuming any food served onboard.[6] Approximately 1 of 8 people with peanut allergy have reported no longer flying due to fear of exposure while onboard an airplane,[6] and these fears are not unwarranted. Close to half of fatal food allergy reactions are triggered by food consumed away from the home, and most reactions occur from foods not thought to contain the allergen.[7]

In addition to venturing outside home, strict avoidance must be maintained within the home. Although common household cleaning supplies will reliably remove peanut allergens from tabletops, dishwashing liquid alone will not.[8] Similarly, hand soap and commercial wipes will remove peanut allergen from skin, but antibacterial hand sanitizer will not.[8] When preparing food in the home, individuals and parents of children with peanut allergy must be careful not to cross-contaminate preparations and must carefully check food labels for allergens. The Food Allergen Labeling

and Consumer Protection Act of 2004 requires that all food labels clearly identify the food source names of all ingredients that are or contain any protein derived from the 8 most common allergens, which are milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans.[9]

Regardless of labeling mandates, cross-contamination within the manufacturing setting is still a risk, and the disclosure of this risk on labeling remains voluntary.[9] The wording of these precautionary labels is not standardized ("may contain [allergen]," "manufactured on shared equipment with [allergen]," "manufactured in the same facility with [allergen]," etc), yet studies have shown that individuals often ascribe a differing amount of risk based on the wording used.[10] Managed care professionals should be aware of potential misconceptions about avoidance and food labels as well as common myths and key messages, as shown in **Table 1**.[10]

Although avoidance is necessary to minimize the risk of exposure to an antigen, it is difficult to accomplish in day-to-day life, and severe reactions frequently occur despite significant efforts.[11] Several challenges must be overcome to achieve effective avoidance, including understanding food labels, overcoming embarrassment (adults) and potential bullying (children) in social situations, failing to recognize actual risk, and preventing cross-contamination in the home. These issues should routinely be addressed in clinical practice with patients who have peanut allergy, and with their families.

Anaphylaxis

Anaphylaxis is a life-threatening emergency requiring immediate intervention.[12] Although death is rare, it can occur and has occurred despite immediate epinephrine (adrenaline) use. Guidelines from the World Allergy Organization (WAO) recommend epinephrine as first-line treatment for anaphylaxis.[13] Epinephrine has 3 primary mechanisms of action in anaphylaxis: (1) alpha-1 agonist vasoconstrictor effects prevent and relieve airway edema, hypotension, and shock; (2) β-1 agonist chronotropic and inotropic effects increase the rate and force of cardiac contractions; and (3) β-2 agonist effects lead to bronchodilation and decreased mediator release.[13] Epinephrine is the only agent that has been shown to decrease hospitalizations and death in individuals experiencing an anaphylactic reaction.[13] Usually administered through an epinephrine autoinjector, early injection of epinephrine (ie, before arrival to the emergency department [ED]), has been shown to reduce the odds of hospitalization compared with late administration (odds ratio [OR], 0.25; 95% CI, 0.12-0.49).[14] Most importantly, delay in epinephrine administration has been associated with food allergy-induced fatalities.[12]

The use of an epinephrine autoinjector has been associated with fewer adverse events (AEs) compared with intravenous (IV) bolus administration of epinephrine.[15] An observational study by Campbell et al evaluated outcomes between routes of epinephrine administration in an ED setting.[15] Of 573 patients, 4 overdoses occurred, all with patients who received IV bolus epinephrine. Furthermore, cardiovascular AEs were seen in 10.0% of patients receiving IV bolus epinephrine compared with just 1.3% of patients using an epinephrine autoinjector (OR, 8.7; 95% CI, 1.8-40.7; $P = .006$).[15] Therefore, extreme caution is recommended when using IV bolus epinephrine.[13]

For adults, the dosage of epinephrine for anaphylaxis is 0.2 to 0.5 mg (0.2 to 0.5 mL of 1 mg/mL solution) intramuscularly (IM) or subcutaneously (SC) every 5 minutes as needed.[16] For IV administration, the dose is 1 mg (1 mL of 1 mg/mL solution) in 250 mL of dextrose sodium chloride (4 mcg/mL) infused at 1 mcg/min (15 mL/h) or 1 mg in 100 mL of normal saline (10 mcg/mL) infused at 5 to 15 mcg/min (30 to 100 mL/h).[16] In children, the dose is 0.01 mg/kg (0.01 mL/kg of 1 mg/mL solution) or 0.3 mg/m^2 SC to a maximum dose of 0.5 mL, which can be repeated every 4 hours if required.[16] Epinephrine autoinjectors are available in 0.1-, 0.15-, and 0.3-mg doses and may be injected SC or IM; doses may be repeated if severe anaphylaxis persists.[16] This is a summary of dosages, and full dosing guidelines should be reviewed for complete recommendations.

The correct use of epinephrine autoinjectors is a critical aspect in the management of care for patients with allergies. Bonds et al found that among 102 patients using epinephrine autoinjectors, just 16% administered the epinephrine correctly; of the remaining 84%, 56% missed 3 or more steps in the administration process.[17] Errors included not holding the unit in place for 10 seconds after triggering (76% made this mistake), failure to place the needle end of the device on the thigh, and failure to depress the device forcefully enough to activate the injection.[17] When counseling on the use of epinephrine autoinjectors, managed care professionals should ensure that the patient

TABLE 1. Myths and Reality of Food Allergens[10]

Myth	Reality
Casual contact or inhalation of dust or vapors from peanut-containing product is a hazard.	The risk of a systemic reaction to a food allergen is primarily through ingestion, with contact and inhalation exposures being low risk.
It is dangerous for individuals with peanut allergy to ingest highly refined commercial peanut oil.	Oils derived from foods can differ in their protein content, based on the refining process, with full refining of oils leading to complete protein removal and tolerance among individuals with food allergies.
Products with precautionary labeling statements carry high risk of cross-contamination.	Actual risk varies but has been found to be higher in products with precautionary labeling. Counseling on accurate interpretation of food labels is essential, with the knowledge that precautionary allergen labeling is not standardized.

Adapted from Egan M, Greenhawt M. Common questions in food allergy avoidance. *Ann Allergy Asthma Immunol*. 2018;120(3):263-271.

and/or caregiver is aware of potential AEs (eg, palpitations, pale skin, sweating, nausea, vomiting, asthenia, dizziness, headache, tremor, and anxiety), how to recognize injection-site infections, and the importance of holding the leg of young children firmly during injection to prevent injury.[16] Patients and caregivers should be advised to seek medical assistance after use, even if symptoms have subsided.[16]

Along with ensuring the proper administration technique, proper storage of epinephrine autoinjectors is also essential. Injectors should be kept at 20° C to 25° C (68° F-77° F) to protect the epinephrine from degradation; freezing for a few days is acceptable, although the solution must be thawed completely before use.[13]

Second- and third-line therapies for anaphylaxis include H_1-antihistamines, H_2-antihistamines, and glucocorticoids.[13] It is important to understand that none of these agents should be used alone for anaphylaxis because these therapies are primarily prophylactic and supportive and are *not* lifesaving.[13] Following an anaphylactic reaction, patients should be referred to an allergy/immunology specialist to accurately diagnose the trigger and provide long-term management.[13]

Emerging Therapies

There are a number of therapies currently under investigation for desensitization of peanut protein. To best understand the clinical data regarding the safety and efficacy of these agents, knowledge of best practice guidelines and common terminology is essential. These standards are summarized below, followed by an overview of the agents currently undergoing development for use in patients with peanut allergy.

PRACTALL Food Challenge Recommendations for Clinical Trials

When evaluating clinical trials involving patients with peanut allergy, managed care professionals should be aware of study design methodology and outcome definitions. Published in 2012 by the American Academy of Allergy, Asthma & Immunology (AAAAI) and European Academy of Allergy and Clinical Immunology (EAACI), the PRACTALL guidelines provide standardized recommendations for the performance of double-blind, placebo-controlled food challenges (DBPCFCs), which are considered the gold standard.[18] Although some trials have successfully incorporated DBPCFCs into their methods, others have not, and recognition of these differences is important to interpreting outcomes.

The PRACTALL guidelines recommend escalating food protein doses in set amounts beginning at 1 mg and escalating up to 3000 mg (ie, 1, 3, 10, 30, 100, 300, 1000, and 3000 mg) or until a reaction occurs.[18] For scale to real-world dosages, a single peanut kernel contains approximately 250 to 300 mg of peanut protein, and a peanut pod contains 2 kernels.[19] Because clinical trial designs vary, understanding the definitions of each outcome that may be reported is important for comparing efficacy data between trials. Managed care professionals should be aware of common descriptors used throughout allergy studies, as defined in **Table 2**.[18] For example, if a trial participant experiences an objective reaction at 100 mg, that would be referred to as the eliciting dose.[18] The cumulative tolerated dose would be 44 mg, the successfully consumed dose would be 30 mg, and the cumulative reactive dose would be 144 mg.[18] Awareness of these definitions is important because Trial 1 may report a cumulative reactive dose of 144 mg, whereas Trial 2 may report a cumulative tolerated dose of 44 mg; without awareness of definitions, the reader could interpret Trial 1 as being more effective than Trial 2, when, in reality, the trials are reporting the same outcome.

Novel Immunotherapies

Several new therapies are undergoing clinical development for use in patients with peanut allergy, and managed care professionals should be knowledgeable about the safety and efficacy of these agents. Although the mechanisms of action of clinical immune tolerance are not completely understood, several theories have been presented in the literature. As summarized by Syed et al, these mechanisms may include increases in allergen-specific blocking immunoglobulin G antibodies, a shift from a T helper type 2 response toward a T helper type 1 response with increased IFN-γ production, reduction in specific immunoglobulin E, reduced recruitment of or increased anergy/deletion of T effector cells, and induction of

TABLE 2. Common Descriptors Used in Allergy Studies[18]

Descriptor	Definition
Cumulative reactive dose	The sum of doses consumed, including the eliciting dose.
Cumulative tolerated dose	The sum of the tolerated doses. Does not include the eliciting dose.
Desensitization	A state in which the patient does not react to ingestion (or just reacts at a higher dose) while on therapy.
Eliciting dose	The dose given during a food challenge that induces the onset of allergic reactions sufficient to stop the challenge.
Successfully consumed dose	The highest dose given during a food challenge that elicits either no symptoms or symptoms that are not clearly indicative of an allergic reaction.
Sustained unresponsiveness	The maintenance of desensitization after a period of abstinence from therapy (weeks to months).
Tolerance	A presumably permanent state in which the subject is able to ingest the food ad lib without reaction indefinitely.

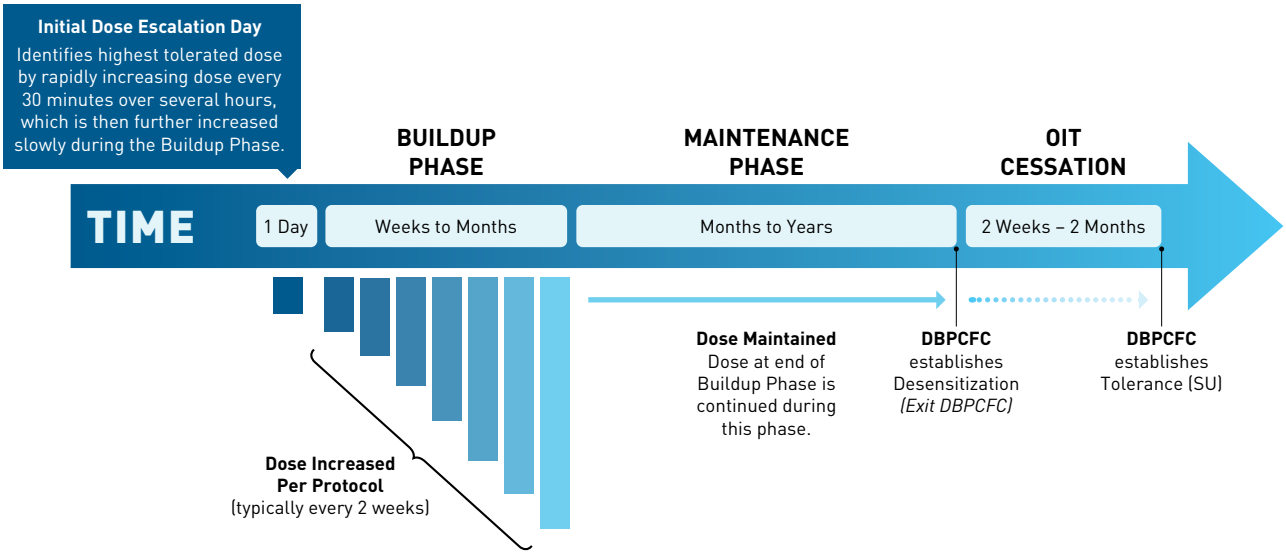
regulatory T cells.[20] Novel immunotherapeutic options undergoing development differ by routes of administration and include oral immunotherapy (OIT), epicutaneous immunotherapy (EPIT), and sublingual immunotherapy (SLIT). Additionally, some biologic agents already approved for use in other diseases are also being explored. The most recent safety and efficacy data on these agents are summarized below.

Oral Immunotherapy

OIT involves exposing a patient with peanut allergy to orally administered doses of an allergen with a goal of inducing desensitization.[21] The typical process is shown in the **Figure**.[22] Although success has been shown using OIT for peanut allergy,[21,23-28] several factors have kept it from being recommended for routine clinical practice.[21] Many early trials did not include standardized entry-and-exit DBPCFCs. AEs are very common and range from mild symptoms to anaphylaxis and persistent gastrointestinal (GI) symptoms. Dropout rates are frequently quite high, often due to these GI symptoms, and low rates of sustained unresponsiveness show that the treatments studied must be continued indefinitely to ensure ongoing desensitization. Phase 3 trials are currently ongoing for AR101, a novel oral agent containing a characterized peanut protein profile; these trials incorporate the PRACTALL guideline standards and may overcome many of the limitations seen in prior studies.[21]

A phase 2 study evaluated the safety and efficacy of AR101 at a maintenance dose of 300 mg daily compared with placebo in 55 patients with peanut allergy who had a cumulative tolerated dose less than or equal to 143 mg (100-mg single dose) of peanut protein in a screening DBPCFC, which followed PRACTALL guidelines and started patients at a dose of 3 mg.[21] The primary end point was the proportion of patients able to achieve a cumulative tolerated dose of greater than or equal to 443 mg (300-mg successfully consumed dose) peanut protein during the exit DBPCFC.[21] Importantly, the exit DBPCFC consisted of doses of 3, 10, 30, 100, 300, and 600 mg given consecutively, as tolerated, 20 to 30 minutes apart; this exit DBPCFC led to a maximum possible cumulative tolerated dose of 1043 mg.[21] In the final intent-to-treat analysis, 79% and 62% of patients treated with AR101 were able to tolerate cumulative tolerated doses of greater than or equal to 443 mg and 1043 mg, respectively, compared with just 19% and 0% of patients given placebo (≥443 mg cumulative tolerated dose: 79% vs 19%; P <.0001; 1043 mg cumulative tolerated dose: 62% vs 0%; P <.0001).[21] Furthermore, reactions upon exit DBPCFC were less severe in the treatment group. Regarding the safety profile of AR101, 97% of patients in the AR101 group (n = 28/29) and 85% of patients in the placebo group (n = 22/26) experienced AEs. During the course of treatment, patients receiving AR101 experienced a total of 413 treatment-emergent adverse events (TEAEs) (35.9 TEAEs per year of exposure), and patients receiving placebo experienced a total of 135 TEAEs (12.1 TEAEs per year). In the AR101 group, 96% of TEAEs were considered mild; the remaining 4% were moderate and included urticaria, pruritus, vomiting, abdominal pain, gastritis, and anaphylaxis.[21] These AEs are similar to those reported in prior studies.[29]

FIGURE. Typical Protocol of OIT Testing in Clinical Trials[22]



DBPCFC indicates double-blind, placebo-controlled food challenge; OIT, oral immunotherapy; SU, sustained unresponsiveness.
Adapted from Gernez Y, Nowak-Wegrzyn A. Immunotherapy for food allergy: are we there yet? *J Allergy Clin Immunol Pract*. 2017;5(2):250-272. doi: 10.1016/j.jaip.2016.12.004.

Six participants receiving AR101 withdrew prematurely due to TEAEs, primarily GI AEs; indeed, GI events occurred in 66% of patients receiving AR101 compared with 27% of those receiving placebo.[21]

Three phase 3 trials of AR101 are currently ongoing or have been recently completed. The PALISADE trial enrolled 551 participants aged 4 to 49 years in the United States, Canada, and Europe.[30] The inclusion criteria limited enrollment to patients who reacted to less than 100 mg of peanut protein during the screening DBPCFC; once enrolled, participants were randomized in a 3:1 ratio to receive AR101 or placebo. The primary efficacy end point was the proportion of participants aged 4 to 17 years tolerating a single highest dose of 600 mg of peanut protein, which equates to a cumulative tolerated dose of 1043 mg.

Results from this trial were announced at the 2018 AAAAI/WAO Joint Congress and updated at the 2018 EAACI Congress.[31] After approximately 1 year of treatment, 67.2% of patients aged 4 to 17 years receiving AR101 tolerated at least a 600-mg successfully consumed dose in the exit DBPCFC compared with just 4.0% of patients receiving placebo (P <.00001). The lower 95% CI between the treatment arm and primary end point was 53%, which greatly exceeded the 15% prespecified threshold (P <.00001).[31] TEAEs occurred in 99% and 95% of AR101 and placebo groups, respectively. AEs that led to study withdrawals among 12.4% of the AR101 group included GI (6.7%), systemic hypersensitivity (2.7%), respiratory system (1.1%), and cutaneous (0.8%) reactions.[31] In addition to the PALISADE trial, the RAMSES open-label extension study (NCT03337542) and ARTEMIS trial (NCT03201003) are underway, evaluating the use of AR101 in the United States, Canada, and Europe.[32,33]

Epicutaneous Immunotherapy

Like OIT, EPIT works by exposing the patient to peanut protein in order to induce desensitization. However, unlike OIT, EPIT is delivered through skin contact via an epidermal patch. Notably, use of EPIT on intact skin does not introduce the allergen into the bloodstream; instead, the intact skin exposure allows allergen uptake by Langerhans cells in the epidermis, which subsequently induce regulatory T cells in regional lymph nodes, leading to downregulation of Th2 responses.[34,35] This contrasts with peanut exposure through inflamed, eczematous skin in patients with atopic dermatitis, which is believed to lead to allergic sensitization.

Viaskin Peanut is an EPIT system currently undergoing phase 3 trials for use in children and adults with peanut allergy.[36,37] In a phase 2 trial, 74 patients aged 4 to 25 years were randomized in a 1:1:1 ratio to receive either 100-mcg or 250-mcg doses of Viaskin Peanut (VP100 or VP250, respectively) or placebo for 52 weeks.[34] The primary outcome was defined as passing a cumulative tolerated dose of 5044 mg during the exit DBPCFC or achieving a 10-fold or greater increase in successfully consumed dose from baseline to week 52.[34] Part of the inclusion criteria required a cumulative reactive dose of 1044 mg or less, as determined by an entrance DBPCFC. A modified PRACTALL protocol was used to conduct DBPCFC at baseline and at 52 weeks, with escalating doses administered every 15 minutes during each DBPCFC.[34]

At study completion, the primary end point was achieved in 46% and 48% of patients receiving VP100 and VP250, respectively (VP100, P = .005; VP250, P = .003), compared with 12% of those receiving placebo.[34] Median changes in successfully consumed doses of peanut protein were 43, 130, and 0 mg in the VP100, VP250, and placebo groups, respectively (VP100 vs placebo, P = .014; VP250 vs placebo, P = .003).[34] AEs predominantly included local patch site (80% of VP100 and VP250 groups; 14% of placebo) and mild systemic reactions (≤0.2% among all groups).[34] In a phase 1b safety study, 52.5% and 45% of participants receiving Viaskin Peanut and placebo, respectively, reported at least 1 TEAE during the study; the most common TEAEs associated with Viaskin Peanut use were local erythema, pruritus, edema, and urticaria.[35]

A phase 2b study evaluated the use of Viaskin Peanut in 221 patients after 12 months of therapy.[38] PRACTALL criteria were used for conducting DBPCFCs before initiating therapy and following 12 months of daily patch applications.[38] The primary efficacy end point of treatment response was defined as 10-fold or greater increase in eliciting dose and/or reaching 1000 mg or greater of peanut protein.[38] By study completion, a significant difference in response rates was seen with the VP250 group versus placebo (absolute difference, 25%; 95% CI, 7.7%-42.3%; P = .01); however, there was no significant difference found between the VP100 and placebo groups. The proportion of patients in the VP250 and placebo groups with an eliciting dose of 1000 mg or greater after 12 months were 32.1% and 12.5%, respectively.[38] In both the Jones et al and Sampson et al trials, the efficacy of Viaskin Peanut was greatest in younger subjects (aged 4-11 years in Jones et al; aged 6-11 years in Sampson et al). Therefore, all subsequent studies have enrolled younger subjects.

In late 2017, topline results were announced for the PEPITES phase 3 trial (NCT02636699), which evaluated Viaskin Peanut in 356 patients aged 4 to 11 years.[37] Treatment responses were defined as eliciting doses of 300 mg or greater or 1000 mg or greater of peanut protein in patients with baseline eliciting doses of 10 mg or less or greater than 10 mg, respectively.[37] After 12 months of treatment, significantly more patients in the VP250 group achieved a response compared with placebo (absolute difference, 21.7%; 95% CI, 12.4%-29.8%; P = .00001). However, the difference in response rates for the primary end point did not reach the 15% lower bound of CI that was proposed in the study's Statistical Analysis Plan submitted to the FDA.[39] Despite this setback, a press release from February 2018 announced that the FDA agreed that the safety and efficacy data for Viaskin Peanut support the submission of a Biologics License Application (BLA) for the treatment of peanut allergy in patients

aged 4 to 11 years.[40] The phase 3 EPITOPE trial (NCT03211247) has begun enrolling subjects aged 1 to 3 years.[36]

Sublingual Immunotherapy

Sublingual immunotherapy (SLIT) involves the administration of small amounts (mcg to mg) of allergen extract under the tongue, where oral Langerhans cells take up the antigen and have been shown to have tolerogenic properties. The use of SLIT has been shown to be effective with few systemic reactions.[41] A 6-month trial of SLIT enrolled 18 children aged 1 to 11 years and randomized them in a 1:1 ratio to receive peanut SLIT or placebo. Inclusion criteria required a peanut-specific immunoglobulin E level of 7 kU/L or greater and a physician-documented history of peanut allergy. After a dose escalation period of 13 weeks, followed by a baseline DBPCFC, all patients received a maintenance dose of 2000 mcg of peanut protein for approximately 6 months before undergoing an exit DBPCFC. The maximum cumulative dose administered during the DBPCFC was 2500 mg of peanut protein.[42] By the end of the study, researchers found that those who were administered SLIT were able to safely ingest 20 times more peanut protein than those in the placebo group (median 1710 mg vs 85 mg; $P = .011$). The most common AE associated with SLIT was transient oropharyngeal itching, which occurred with 9.3% of doses administered.[41]

Fleischer et al evaluated the safety and efficacy of SLIT in 40 patients aged 12 to 37 years.[42] The primary end point was the proportion of patients able to pass a DBPCFC after 44 weeks of treatment. A treatment response was defined as successful consumption of 5 g of peanut powder (≈50% peanut protein) or achievement of a 10-fold increase in the amount of peanut powder consumed compared with baseline.[42] Subjects had a baseline median successfully consumed dose of 46 mg of peanut powder (≈23 mg peanut protein); 70% of participants receiving SLIT were responders at 44 weeks compared with 15% of those receiving placebo ($P < .001$), with a median successfully consumed dose of 496 mg among responders. By 68 weeks of SLIT, median successfully consumed dose increased to 996 mg, a significant change from week 44 responders ($P = .05$).[42] Although 63.1% of participants were symptom-free at 44 weeks, the 3-year extension arm of this study reported that more than 50% of participants dropped out, largely due to difficulty maintaining the daily dosing.[43]

Three clinical trials (NCT01373242, NCT02304991, and NCT03463135) are ongoing, evaluating SLIT in patients with peanut allergy.[44-46] The most advanced stage of development is a phase 2 trial that has an expected completion in May 2020.[45]

OIT, EPIT, and SLIT: Efficacy Versus AEs

When comparing novel immunotherapies, managed care professionals will need to weigh the efficacy of OIT, EPIT, and SLIT against the risk of AEs associated with each of these therapies. To interpret efficacy, it must be decided how much desensitization is clinically relevant. **Table 3** provides a summary of current comparisons among OIT, SLIT, and EPIT from clinical trials.[22]

A recent analysis estimated that increasing the threshold of reactivity to peanut from a baseline of 100 mg or less to 300 mg would reduce the risk of accidental reactions caused by contaminated foods (most often cookies, ice cream, and snack chip mixes) by more than 95%.[47] Narisety et al compared SLIT with OIT in 16 participants aged 7 to 13 years.[48] Doses were escalated to 3.7 mg/day (SLIT) or 2000 mg/day (OIT), and DBPCFCs were conducted at 6 and 12 months of therapy. After 12 months, all participants had a 10-fold increase in challenge threshold; however, the threshold was significantly higher among participants receiving OIT compared with those receiving SLIT (141-fold vs 22-fold; $P = .01$).[48] AEs were also more common with OIT compared with SLIT (43% vs 9% of doses; $P < .001$), with 5 doses of epinephrine required to treat systemic reactions in 4 subjects receiving OIT.[48] The main takeaway from these trials is that SLIT is effective at inducing desensitization, albeit not as effective, but with fewer AEs compared with OIT.

A recent review by Dulmi et al evaluated 12 articles reporting outcomes from trials of OIT or EPIT.[49] Pooled studies of OIT included a total of 188 participants at trial start, with 122 remaining in active status by end of study (35% dropped out). EPIT studies had a pooled 295 participants at trial start, with 273 remaining in active status by end of study (7.5% dropped out).[49] The number of participants who achieved successful OIT or EPIT results were 71% and 56%, respectively, indicating that, although EPIT yields fewer dropouts, OIT is more effective at inducing desensitization.[49]

Despite being more efficacious, OIT has demonstrated concerning rates of AEs in clinical trials. Virkud et al pooled data from 3 OIT studies involving 104 children with peanut allergy to evaluate safety outcomes and identify potential baseline predictors of higher rates of AEs.[29] Researchers found that 80% of participants experienced likely related AEs during OIT, with 42% experiencing systemic reactions and 49% experiencing GI symptoms.[29] Baseline allergic rhinitis (incidence rate ratio [IRR]: 2.85; 95% CI, 1.61-5.04; $P < .001$), asthma (maintenance phase only, IRR: 2.30; 95% CI, 1.08-4.88; $P = .03$), and peanut skin-prick test (IRR: 1.38; 95% CI, 1.10-1.72; $P = .005$) significantly predicted higher rates of AEs.[31] Eosinophilic esophagitis is estimated to occur in about 2.7% to 5% of patients undergoing OIT.[50,51]

Currently, both AR101 and Viaskin Peanut are in the process of submitting BLAs to the FDA. The relative pros and cons of each treatment will need to be weighed when choosing which therapy is most appropriate for an individual patient. For example, for a child with a history of eosinophilic esophagitis or chronic abdominal symptoms, the clinician may need to take into consideration the safety data of AR101. For other patients, the relative increased efficacy of AR101 may outweigh the higher rate of AEs.

TABLE 3. Comparison of OIT, SLIT, and EPIT[22]

	OIT	SLIT	EPIT
Daily maintenance dose	300-4000 mg	2-7 mg	50-500 mcg, usually 250 mcg
Specific foods studied	Peanut, cow's milk, egg, wheat	Peanut, cow's milk, hazelnut, peach	Peanut, cow's milk
Observed dosing	Up-dosing every 1 or 2 weeks	Up-dosing every 1 or 2 weeks	Initiation and periodic observation
Safety	Less desirable	More desirable	More desirable
AEs			
Oral	Frequent, mild oropharyngeal pruritus	Majority of AEs are oropharyngeal (local)	None reported
Skin	Yes (urticaria)	Yes (urticaria)	Yes (local skin reactions: eczema, urticaria)
GI	Yes, most AEs are GI (abdominal pain, nausea)	Rare, less common	Rare, ongoing investigation
Severity/systemic/ anaphylaxis	Can be systemic when associated with exercise, fever, URI, menstruation, dosing on empty stomach	Mild, rare systemic reactions	Mild local reactions
Eosinophilic esophagitis	Estimated at 2.7%-8%	Not reported	Not reported
Frequency of AEs	Almost everyone will react during the escalation phase	Less frequent	Reaction frequencies range from 0.1%-84%
Activity restriction	Dose taken with meal; no physical activity for 2 hours after dose administration; withhold with illness	Do not eat for 30 minutes after dose administration	None
Efficacy	More desirable	Less desirable	Ongoing investigation
Desensitization (intent-to-treat analysis)	Large effect (usually, the patients who finish the protocol achieve desensitization) 62%-100%	Moderate effect 10.8%-70%	Ongoing investigation 46%-48%
Sustained unresponsiveness	50%-79%	10%-100%	No data
Long-term tolerance	Variable response	Ongoing investigation	Present
Immunomodulation	Significant	Present	Present

AE indicates adverse event; EPIT, epicutaneous immunotherapy; GI, gastrointestinal; OIT, oral immunotherapy; SLIT, sublingual immunotherapy; URI, upper respiratory infection.
Adapted from Gernez Y, Nowak-Wegrzyn A. Immunotherapy for food allergy: are we there yet? *J Allergy Clin Immunol Pract.* 2017;5(2):250-272. doi: 10.1016/j.jaip.2016.12.004.

Monoclonal Antibodies

Several monoclonal antibodies are undergoing clinical trials for use in patients with peanut allergies, including omalizumab, dupilumab, and a novel agent, ANB020. Omalizumab is a monoclonal anti-immunoglobulin E antibody, initially approved for the treatment of asthma, which is undergoing clinical trials as a facilitator for rapid desensitization when given alongside OIT.[52] After 12 weeks of receiving omalizumab or placebo, 37 participants underwent a rapid 1-day desensitization of up to 250 mg of peanut protein followed by weekly increases up to 2000 mg. Participants then underwent challenges of 4000 mg peanut protein.[52] At study entry, all participants demonstrated significant reactions during DBPCFCs to a peanut protein dose of 50 mg or less (88 mg cumulative tolerated dose). By study completion, the median peanut dose tolerated on the initial desensitization day was 250 mg for participants receiving omalizumab compared with 22.5 mg for those receiving placebo. Six weeks after stopping omalizumab, 79% of participants receiving omalizumab tolerated 2000 mg of peanut protein compared with 12% of those receiving placebo (P <.01).[52] Rates of adverse reactions were similar between omalizumab and placebo groups, despite the omalizumab group receiving higher doses of peanut.[52]

Dupilumab, a monoclonal antibody that inhibits interleukin-4 (IL-4) and IL-13 by binding to the IL-4 receptor alpha, will begin a clinical trial in conjunction with AR101 in 2018 to investigate its efficacy in rapid desensitization when combined with OIT.[53] Interestingly, dupilumab has shown promise in treating eosinophilic esophagitis in adults, according to data presented at the American

College of Gastroenterology 2017 conference, and, therefore, theoretically may reduce incidence of GI symptoms and eosinophilic esophagitis in those undergoing OIT.[54]

Unlike omalizumab and dupilumab, ANB020, a monoclonal antibody that inhibits IL-33, is undergoing a phase 2 trial (NCT02920021) for stand-alone immunotherapy similar to OIT, EPIT, and SLIT.[55] In March 2018, researchers announced interim results from a phase 2a study evaluating the safety and efficacy of a single dose of ANB020 compared with 3 doses of placebo in 20 adults with peanut allergy and a history of anaphylaxis.[56] All participants underwent DBPCFCs per PRACTALL guidelines at baseline and demonstrated dose limiting at or before a cumulative dose of 500 mg of peanut protein. By the 14-day DBPCFC, 46% of treated patients with moderate to severe symptoms at baseline demonstrated improved peanut tolerance compared with 0% of those receiving placebo.[56] Concomitant allergic symptoms, including urticaria, pruritus, rhinitis, asthma flares, and other nut allergies, occurred in 80% of participants receiving placebo but just 7% of those receiving ANB020. There were no dropouts during the study at the time of interim analysis, with the most common TEAE reported among 4 of 15 patients receiving ANB020 being mild to moderate headaches.[56]

Conclusions

Treatment for peanut allergy relies heavily on avoidance and prompt administration of epinephrine if and when anaphylaxis occurs. To address the need for better therapies that can aid in improving long-term outcomes, several novel immunotherapies (OIT, EPIT, SLIT, and monoclonal antibodies) are undergoing clinical evaluation for children and adults with peanut allergy. Comparatively, OIT appears to offer the greatest advantages in efficacy regarding induced desensitization; however, OIT also presents the highest rates of AEs. It is also important to recognize that the treatments under investigation aim to protect from accidental ingestion leading to allergic reactions, not to allow full reintroduction of peanut into the diet. Understanding the PRACTALL guidelines and outcome definitions is critical in comparing results between trials, and managed care professionals must be prepared to translate these results into clinical practice and future pharmacy benefit decision making. ■

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