

Current and Future Treatment of Peanut Allergy



Brian P. Vickery, MD^a, Motohiro Ebisawa, MD, PhD^b, Wayne G. Shreffler, MD, PhD^c, and Robert A. Wood, MD^d *Atlanta, Ga; Sagamihara, Japan; Boston Mass; and Baltimore, Md*

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List of Design Committee Members: Brian P. Vickery, MD, Motohiro Ebisawa, MD, PhD, Wayne G. Shreffler, MD, PhD, and Robert A. Wood, MD (authors); Michael Schatz, MD, MS (editor)

Learning objectives:

1. To describe the appropriate use of skin prick tests, peanut- and component-specific IgE, and oral food challenges in the diagnosis of peanut allergy.
2. To understand the evidence emerging from clinical trials of oral and epicutaneous immunotherapy and explain how these modalities may be used in the treatment of future patients.
3. To recognize remaining knowledge gaps in peanut allergy and identify promising investigational approaches.

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^aEmory University School of Medicine, Atlanta, Ga

^bSagamihara National Hospital, Sagamihara, Japan

^cMassachusetts General Hospital and Harvard Medical School, Boston, Mass

^dJohns Hopkins University School of Medicine, Baltimore, Md

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Corresponding author: Brian P. Vickery, MD, Emory University School of Medicine, 2015 Uppergate Dr, NE, Atlanta, GA 30322. E-mail: bpvicke@emory.edu. 2213-2198

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Based on productive translational research programs conducted over the last 20 years, the clinical landscape of peanut allergy is now rapidly changing. In this review, we review data from recent trials of investigational peanut oral and epicutaneous immunotherapies, explore the pipeline of novel therapies in early development, and identify future research needs and priorities. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:357-65)

Key words: Peanut allergy; Anaphylaxis; Quality of life; Desensitization; Sustained unresponsiveness; Tolerance

INTRODUCTION

Evidence suggests that the prevalence of peanut allergy has been rising in recent years and now may affect as many as 1.5% of US children.¹ Similar trends have been observed in other industrialized nations. Historically, the standard of care for

Abbreviations used

AE- adverse event
AIT- allergen immunotherapy
DBPCFC- double-blind, placebo-controlled food challenge
ED- eliciting dose
FAHF-2- Food Allergy Herbal Formula-2
FDA- Food and Drug Administration
GLA- Glucopyranosyl Lipid A
OIT- oral immunotherapy
PE- peanut extract
RCT- randomized controlled trial
RR- risk ratio
SLIT- sublingual immunotherapy
SU- sustained unresponsiveness

peanut allergy has been a strict elimination diet and timely administration of rescue medications in case of an allergic reaction upon accidental exposure. Yet peanut allergy is typically characterized by sensitivity to small exposures, persistence into adulthood, and risk of severe reactions, perhaps in part due to the unique potency of peanut proteins and their widespread distribution in the environment. Major recent developments in biomedical research have informed our understanding of the disease and yielded new treatment options on the cusp of regulatory approval as well as a pipeline of next-generation therapies currently in early-stage development. This review will discuss the current and future landscape of peanut allergy treatments and identify the remaining key gaps to be addressed with future research.

FIRST-GENERATION THERAPIES

Overview/history

The history of peanut allergy treatment has been dominated by allergen-specific immunotherapy (AIT). Most reviewers trace the current origins of peanut allergy treatment to the efforts of Oppenheimer et al² and Nelson et al³ to apply subcutaneous immunotherapy protocols widely used for the treatment of environmental allergies in the 1990s, which were associated with unacceptably high rates of adverse events (AEs). This experience, in part, led to the adoption of alternative routes of allergen delivery, including mucosal and epicutaneous, which have now progressed to the point of phase 3 trials led by new commercial entities.

Outcomes and end points of immunotherapy

Because individuals with IgE-mediated peanut allergy are subject to the pathophysiological consequences of their condition only when accidental exposures occur, and are otherwise peanut symptom-free, the burden of disease is highly dependent on the impact to patients' quality of life from living with and mitigating the risk of such exposures. Both the actual and perceived risk of these exposures varies enormously among patients, and therefore how an individual weighs the benefit/risk equation of treatment is also likely to vary considerably.⁴ For example, patients who seek out immunotherapy treatment are reported to be more anxious about their disease and fearful of death,⁵ and may not adequately estimate the actual risk of death.⁶ As new treatments move forward, it

will be critical to monitor psychosocial outcomes to determine whether these burdens are relieved with treatment (Table I).

There are several outcomes that have been considered in the context of food allergy treatment, including desensitization, sustained unresponsiveness (SU), patient-reported outcomes such as quality of life, and reaction severity. No clinical trials have assessed either full tolerance (defined by the Food and Drug Administration [FDA] as "complete and permanent resolution of clinical response following exposure to any amount of the identified allergenic food") or clinical "field efficacy" (defined by the FDA as "the rate and/or severity of reactions to food exposures encountered outside a controlled clinical setting"⁷). Both these outcomes are generally not considered feasible for clinical trials,⁷ but could be a component of postmarketing registry studies. That leaves desensitization, SU, and reaction severity as end points that could be derived using double-blind, placebo-controlled food challenges (DBPCFCs), which along with patient-reported outcomes are most suitable for clinical trials (Table I) although it should be noted that no current patient-reported outcomes were developed to measure treatment effects. Desensitization can be regarded as a transient state of reduced reactivity, measured as an increase in the dose that triggers a convincing reaction during a posttreatment DBPCFC, that would likely offer protection from accidental consumption. However, there is no agreement on how much reactivity should be reduced to confer clinically meaningful protection, and this measure of efficacy is variably measured and variably described in the literature, making direct comparisons difficult. SU refers to a more lasting clinical outcome that leaves the treated patient clinically protected for weeks or months, even in the absence of ongoing dosing. That can be assessed only in those trials that include an allergen avoidance period following treatment and assessment of desensitization. Finally, even the assessment and reporting of safety and tolerability data are not uniform across studies and naturally vary substantially among forms of immunotherapy, adding additional complexity when comparing these treatments. Several anaphylaxis symptom scores exist to score reaction severity,⁸ but the absence of a standardized single scoring system for allergic reaction severity has recently been characterized as an urgent need.⁹

Mechanisms and mechanistic outcomes of AIT are outside the scope of this review, but both cellular and humoral changes to the adaptive immune response have been the primary focus, with subsequent impacts on IgE-mediated effector cell responses, though some effects on innate immunity have also been described and the field is rapidly evolving both to better understand mechanisms of IT action and to identify biomarkers for treatment response.¹⁰⁻²²

ORAL IMMUNOTHERAPY

From 2009 to 2011, there was an initial cluster of reports on the efficacy of oral immunotherapy (OIT) for the treatment of peanut allergy,²³⁻²⁸ incorporating increasingly rigorous study design characteristics, such as randomization, treatment masking, and individual posttreatment assessment using a DBPCFC to more objectively determine efficacy; some but not all studies also used baseline DBPCFCs. These studies have been complemented by additional small, mostly single-center studies, with variable design, including targeted treatment doses, details of

TABLE I. Limitations of current clinically oriented outcomes in peanut allergy studies

Outcome	Limitation(s)	Potential next steps
Desensitization	- Requires oral food challenge - Minimal clinically important difference (MCID) not established - Substantial variability in stopping rules, dose levels, and terminology used for reporting results (eg, tolerated vs eliciting dose)	- Need accurate biomarkers to minimize risk and accelerate research - Key stakeholders should define MCID - Food allergy treatment outcomes and reporting conventions must be harmonized
Sustained unresponsiveness	- All of the same as desensitization, plus: - No consensus on what evidence is needed to distinguish from desensitization	- Workgroup could develop a consensus approach to clinically defining the term - Dietary/follow-up guidelines should be developed - Long-term observational protocols are needed
Immune tolerance	- Requires lengthy observation period after stopping treatment - Control group required to demonstrate causality - No consensus on what evidence is needed to distinguish from SU	- All of the above, plus: - Immunologic signature of true tolerance is needed
Field efficacy	- Accidental exposures can be difficult to detect, especially if treatment renders them silent - Requires large sample, control group, and lengthy observation periods	- Large registry studies with simple, effective (eg, smartphone-based) surveillance systems are needed - HEOR methods analyzing claims data could be helpful - Altering dietary advice (eg, allowing PAL consumption) could be a testable research question
Patient-reported outcomes	- FAQLQ/FAIM are validated but remain primarily research tools and were not developed to measure a treatment effect - No simple wellness tool for use in clinic	- New patient-reported outcome measures that capture the effects of treatment need to be developed and validated for scientific use - A simple, easy-to-use instrument (similar to the Asthma Control Test) should be developed and validated for daily use in the clinic
Safety	- Substantial variation exists in identification and reporting of key safety events - No unified definition of anaphylaxis exists - Multiple grading scales are used to rate severity	- Core set of safety outcomes should be defined - The definitions and severity grading of all allergic reactions including anaphylaxis must be standardized

FAIM, Food Allergy Independent Measure; FAQLQ, Food Allergy Quality of Life Questionnaire; HEOR, health economics and outcomes research; PAL, precautionary allergen labeling.

dose escalation, ages of inclusion, and clinical end points.^{22,29-38} In addition, 1 group has shown that omalizumab can be used to achieve maintenance dose more quickly.^{39,40}

Nurmatov et al⁴¹ reviewed the published literature through March 2016 and published a meta-analysis of the data. On the basis of randomized clinical trials (RCTs) of OIT for treating any food allergy, they found a highly significant effect on desensitization as determined by an exit DBPCFC, favoring those receiving active (432 of 573) versus placebo (44 of 409) (risk ratio [RR], 7; $P < .0001$).⁴¹ Three of the published studies^{27,32,33} that randomized more than 150 patients total met inclusion for review as RCTs of peanut OIT; the RR for these trials ranged from 12 to 50 in favor of desensitization with active treatment. In contrast, there were not enough RCTs evaluating SU following peanut OIT, though they found a trend in favor of active treatment causing SU when evaluating all foods overall (RR, 3.4 [0.9-13; $P = .07$]). From this, as well as from the larger number of nonrandomized studies assessing SU, it is clear that OIT results in SU less frequently than it does in desensitization. To illustrate this, an early study evaluated SU after 5 years of peanut OIT.³¹ This small nonrandomized single-center study found that overall 12 of 39 (31%) OIT-treated individuals developed SU, defined in this study as tolerating 5 g of peanut protein in a DBPCFC conducted 1 month after stopping OIT, whereas 27 of 39 (69%) had achieved desensitization by that

team's definition. Other studies have measured SU at various intervals after OIT discontinuation and found similar trends, leading to the general conclusion that, given enough time, OIT-induced desensitization will eventually be lost after stopping treatment. As a result, OIT should not be considered curative but rather an indefinite form of treatment.

This early-stage evidence spurred an industry-sponsored effort to develop a peanut OIT product manufactured to current Good Manufacturing Practice specifications and intended for commercialization, and a protocol to accompany it. Bird et al⁴² published the phase 2 clinical trial evaluating 55 children, adolescents, and young adults in 8 US centers. The selected maintenance dose was 300 mg, lower than that used in most preceding trials. Inclusion required pretreatment objective clinical reactivity at a maximum single dose of 100 mg in a screening DBPCFC, and the primary end point was the proportion of participants tolerating, with no or mild symptoms, a maximum single dose of 300 mg (cumulative 443 mg) in an exit DBPCFC after 2 weeks of maintenance treatment. Seventy-nine percent of the actively treated subjects in the intent-to-treat analysis tolerated 300 mg posttreatment in comparison to 19% of the placebo-treated subjects ($P < .0001$). Active treatment was also associated with significantly reduced symptom severity of reaction at posttreatment DBPCFC. SU was not evaluated. Six of 29 in the active treatment group withdrew,

including 1 diagnosed with eosinophilic esophagitis, versus 0 of 26 in the placebo group. AEs were common and mild or moderate; there were no investigator-determined severe AEs. Overall, 90% of actively treated subjects experienced a treatment-related hypersensitivity event, compared with 38% of the placebo group. Outside of the DBPCFCs, 1 participant, in the AR101 group, required epinephrine for moderate anaphylaxis that was associated with exercise and occurred 16 hours after the previous dose. Participants were advised to avoid the use of nonsteroidal anti-inflammatory drugs, to refrain from activity for 2 hours postdosing, and to lower dosing around intercurrent illnesses, because these have been identified as cofactors to treatment-related AEs.⁴³ These data led to the first phase 3 clinical trial of OIT, which was recently completed and published in the *New England Journal of Medicine*.⁴⁴ Briefly, this multicenter RCT enrolled 554 peanut-allergic patients aged 4 to 55 years who had objective clinical reactivity at a maximum single dose of 100 mg in a screening DBPCFC, and randomized them 3:1 to active versus placebo. In contrast to the phase 2 study, the primary end point of this trial was tolerating, with no or mild symptoms, greater than or equal to 600 mg single dose in the exit DBPCFC conducted 6 months after achieving a 300 mg maintenance dose. The primary end point of the study was met, with 67% of the actively treated group tolerating greater than or equal to 600 mg in the exit DBPCFC versus 4% of placebo ($P < .0001$). AEs led to withdrawal in 12.4% and 1.6% of active and placebo recipients, and 2.2% and 0.8% had a serious AE, respectively. There was 1 case of eosinophilic esophagitis in the active group.

Sublingual immunotherapy

Published experience of sublingual immunotherapy (SLIT) for peanut allergy is much more limited,⁴⁵⁻⁴⁹ though SLIT has been tested for multiple foods besides peanut, and a consistently positive effect was seen. Two of these studies in peanut allergy^{45,46} met inclusion criteria for the Nurmatov meta-analysis, and each found a statistically significant effect on desensitization favoring SLIT (overall 25 of 31 active vs 3 of 27 placebo; RR, ~7). In a small randomized trial directly comparing SLIT to OIT, there was no between-group difference in the proportions achieving desensitization, defined here as a minimum 10-fold increase in posttreatment threshold.⁴⁸ However, the median cumulative threshold dose among treatment completers increased approximately 20-fold with SLIT and more than 300-fold with OIT. Withdrawal rates with SLIT appeared to be lower and systemic reactions were rarer than with OIT. These safety and efficacy observations in the only comparative peanut AIT study seem generally consistent when reviewing the data from noncomparative SLIT and OIT trials. SLIT may have lost favor based on the results of these comparisons, but when one looks at a bigger picture of the available data, the efficacy of SLIT is quite comparable to that seen with epicutaneous immunotherapy, still with an improved safety profile compared with that of OIT. A novel approach to SLIT using an adjuvanted approach is discussed further below.

Epicutaneous immunotherapy

Epicutaneous immunotherapy for peanut allergy is another approach that has entered late-stage clinical development, with the recent completion of a first phase 3 clinical trial

(clinicaltrials.gov; NCT02636699). The rationale of immunotherapy via this route rested on preclinical animal studies, with recent data implicating the induction of regulatory responses via the unique immunologic milieu of skin hair follicles.⁵⁰ Three clinical trials have been published to date,⁵¹⁻⁵³ 2 of which have evaluated efficacy. The primary phase 2 clinical trial randomized 221 peanut-allergic children, adolescents, and adults who reacted at 300 mg or less of peanut protein in the screening DBPCFC to placebo or 1 of 3 doses (50, 100, or 250 μ g) of a novel transdermal "patch" in equal proportions. The primary end point was the proportion of treatment responders at the 12-month exit DBPCFC, defined as either a 10-fold improvement in eliciting dose (ED) compared with baseline, or an ED of greater than or equal to 1000 mg peanut protein. The absolute difference in the response rates between the 250- μ g patch and the placebo patch was 25% (95% CI, 7.7%-42.3%; $P = .01$; number needed to treat, 4).⁵³ In secondary analyses, effects were found to be strongest in the 6- to 11-year-old group, whereas no differences between active and placebo were seen in adolescents or adults. Treatment-related AEs occurred twice as often with active treatment (~95% vs 48%), mostly skin-related and there were no serious related AEs, but 1 moderate episode of anaphylaxis deemed possibly related. In another phase 2 study carried out by the Consortium for Food Allergy Research,⁵² 100 μ g and 250 μ g active patches were compared with placebo with a similar strategy but measuring the successfully consumed dose at the 12-month exit DBPCFC rather than the ED. The median change in the successfully consumed dose at 12 months was 130 mg for the 250- μ g treatment group ($P = .003$ vs placebo), with a similar safety profile. Based on the phase 2 findings, the 250- μ g dose was selected for the phase 3 trial (clinicaltrials.gov; NCT02636699) in children aged 4 to 11 years. In this recently completed study presented in abstract form at American Academy of Allergy, Asthma, and Immunology 2018⁵⁴ but not yet published, 356 peanut-allergic children who reacted to 300 mg or less of peanut protein in the screening DBPCFC were randomized 2:1 to receive 250 μ g active or placebo patch. The primary end point of the study was the proportion of treatment responders at the 12-month exit DBPCFC, defined as either greater than or equal to 300 mg ED in those with baseline ED of 10 mg or less, or an ED of greater than or equal to 1000 mg in those with baseline ED of more than 10 mg. Response rates were 35.6% in the active group and 13.6% in the placebo group ($P < .0001$), for a between-group absolute difference of 21.7% (95% CI, 12.4%-29.8%). However, the primary end point of the study was not met, because the lower bound of the 95% CI around this between-group difference did not exceed the prespecified minimum of 15%. Longer-term treatment outcomes will be evaluated in ongoing studies.

NEXT-GENERATION THERAPEUTIC APPROACHES

The next generation of potential therapies is rapidly evolving. In fact, some of what we are writing today will be outdated next week. This is an exciting area, combining the best in science with dramatically increasing interest in food allergy from the pharmaceutical industry. In contrast to the primary reliance on transient effector cell hyporesponsiveness in AIT, rational design strategies that target immunologic pathways, perhaps with non-allergen-specific impact, are emerging (Figure 1).

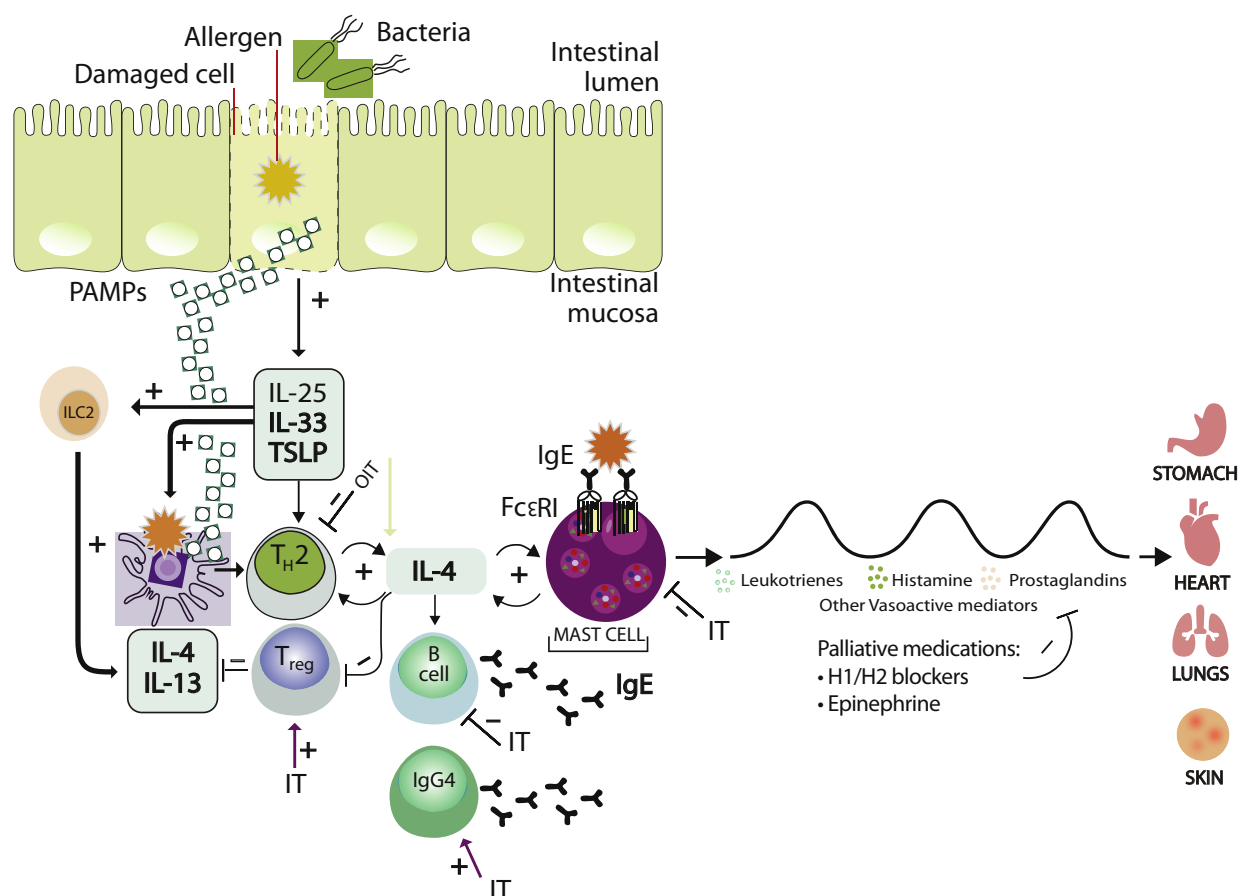


FIGURE 1. Mechanisms of food allergy and its treatment. Signals in the local mucosal microenvironment (tissue damage; dysbiosis) promote the release of the epithelial cytokines interleukin (IL)-25, IL-33, and thymic stromal lymphopoietin (TSLP). These conditions influence antigen presentation and favor the development of innate and adaptive immune responses that promote allergic inflammation (bold arrows), ultimately leading to the production of immunoglobulin E (IgE). IgE sensitizes mast cells by binding to its high-affinity receptor and, when cross-linked upon re-exposure to allergen, causes the release of vasoactive mediators that result in allergic symptoms. Commonly used rescue medications partially palliate these symptoms but do not affect the immune response upstream of sensitized mast cells. However, all forms of AIT studied to date are immunomodulatory and appear to affect the functioning of T and B cells. New biologics are under study in food allergy development programs that target the molecules depicted in bold. *EPIT*, Epicutaneous immunotherapy; *IT*, immunotherapy. Adapted with permission from Renz H, Allen KJ, Sicherer SH, Sampson HA, Lack G, Beyer K, et al. Food allergy. *Nat Rev Dis Primers* 2018;4:17098.

Approaches using modified proteins

One novel approach for the treatment of peanut allergy is based on the potential use of immunotherapy in which the allergenic proteins have been modified, theoretically with the potential to induce desensitization or tolerance without the same risk of IgE-mediated reactions. One such product, referred to as EMP-123, is a rectally administered suspension of recombinant Ara h 1, Ara h 2, and Ara h 3, modified by amino acid substitutions at major IgE-binding epitopes and encapsulated in heat/phenol-killed *Escherichia coli* ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00850668); NCT00850668). In 2013, Wood et al⁵⁵ published results of a phase 1 study of EMP-123, in which 5 healthy volunteers and then 10 peanut-allergic adults were treated. Unfortunately, AEs were common among the peanut-allergic volunteers, including 5 in whom AEs prevented completion of dosing and 2 with anaphylactic reactions.

These results suggested that any future studies using this product would require changes to the allergen modification, dosing scheme, and/or route of delivery.

Another approach to allergen modification uses a chemically modified, aluminum hydroxide-adsorbed peanut extract (PE), HAL-MPE1, that is administered by subcutaneous injection. A first-in-human safety trial with this product was completed in Denmark and a phase 1 trial is currently underway in the United States and Canada ([clinicaltrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02991885); NCT02991885). In the current study, a cohort of peanut-allergic adults will be treated, followed potentially by cohorts of adolescents and then children down to the age of 5 years, with the primary aim of the study to assess the safety and tolerability of incremental doses of HAL-MPE1. Although biomarkers are being assessed, other measures of potential efficacy will await further study if the

TABLE II. New areas for research in the treatment of peanut allergy

Research area	Knowledge gaps
Real-world effectiveness, defined as preventing or mitigating the consequences of accidental exposure	• What are the true risks of accidental exposure and how well do treatments reduce that risk? • Are there patients for whom immunotherapy could substantially increase risk? • Does peanut allergy treatment affect mortality?
Detection of rare safety events in real-world populations	• Do treatments have long-term safety risks different from those observed in clinical trials?
Biological, clinical, and social determinants of treatment response (includes biomarker studies)	• Who responds best to each treatment and why? • Can an accurate biomarker be developed to reduce dependence on OFCs?
Long-term adherence	• How sustainable are indefinite treatment regimens? • What is the best way to encourage adherence? • How does nonadherence or suboptimal adherence impact safety and efficacy?
Impacts of peanut immunotherapy on health economic outcomes	• Is peanut allergy treatment cost-effective? • Does treatment reduce utilization of emergency and/or inpatient services?
Development of patient-centered outcomes research framework, including benefit/risk assessment aids	• What are the preferences of patients and caregivers regarding treatment? • How do patients and caregivers define treatment success? • How best to engage providers and patients about the individuals' assessment of benefit/risk?
Large-scale pragmatic trials and comparative effectiveness studies	• How do peanut allergy treatments compare head-to-head in real-world settings? • Can treatments be combined for superior outcomes? • What is the optimal approach to patient selection?

OFC, Oral food challenge.

phase 1 study is successful in demonstrating a sufficiently reassuring safety profile.

An additional and potentially more elegant approach to the concept of modified allergens, now in human trials after many years of development, is a product composed of synthetic peptides representing T-cell epitope sequences from Ara h 1 and Ara h 2.⁵⁶ It is hypothesized that this product, PVX108, administered by intradermal injection, will have minimal to no IgE binding and thereby produce immune tolerance to peanut proteins with little or no capacity to induce acute allergic reactions. A first-in-human clinical trial is underway to determine the maximum dose that can be safely administered as a single injection, and then to assess the safety of up to 9 escalating doses administered once every 2 weeks (Australia New Zealand Clinical Trials Registry #ACTRN12617000692336).

Probiotics

There is evidence implicating the role of the microbiome in allergic disease,⁵⁷ and a few OIT trials have now used adjunctive probiotics in an effort to enhance desensitization and SU. In 1 study, children with peanut allergy were randomized to receive either peanut OIT combined with the probiotic *Lactobacillus rhamnosus*, or placebo OIT without probiotics, once daily for 18 months. Two to 5 weeks after the end of the trial, 82.1% of the active group members were desensitized to peanut compared with 3.6% in the placebo group.³³ At 4-year follow-up, 70% of children who developed SU passed another challenge test, suggesting that this combination may be effective in inducing longer-term desensitization.⁵⁸ Additional studies are planned to further develop this concept.

Chinese herbal formulas

Food Allergy Herbal Formula-2 (FAHF-2) is a formulation of 9 traditional Chinese herbs. In murine models of food allergy, FAHF-2 appeared efficacious in reducing allergic reactions^{59,60} and also appeared to enhance the effects of OIT.⁶¹ A phase 1

trial of FAHF-2 found it safe and well tolerated, with favorable *in vitro* immunomodulatory effects.⁶² However, no efficacy was observed in a double-blind, placebo-controlled phase 2 trial.⁶³ Additional studies of FAHF-2 as a possible adjunct to multifood OIT and omalizumab are currently underway (clinicaltrials.gov; NCT02879006).

DNA Vaccines

DNA vaccines represent another novel immunotherapeutic approach for the treatment of peanut allergy, with a product referred to as ASP0892 now under human study. In brief, DNA encoding the peanut allergens Ara h 1 to 3 are inserted in tandem in a single plasmid containing the coding sequence for lysosomal-associated membrane protein. Uptake of the plasmid by antigen-presenting cells results in the synthesis of an allergen-lysosomal-associated membrane protein fusion protein, with the hypothesis that T_H1 responses will be induced with little risk of IgE-mediated reactions. This approach has been studied in Japanese red cedar allergy in murine studies that demonstrated induction of robust T_H1-type immune responses,⁶⁴ and in a phase 1 trial that indicated that the vaccine is safe and immunologically active.⁶⁵ A phase 1 study of ASP0892 is currently underway to evaluate the safety, tolerability, and immune responses in peanut-allergic adults (clinicaltrials.gov; NCT02851277). A total of 4 doses are administered once every 2 weeks, with comparisons of low-dose versus high-dose formulations as well as intramuscular versus intradermal delivery.

Biologic therapies

Several biologic therapies are of great interest for the potential treatment of food allergy. First, in addition to the potential use of omalizumab as an adjunct to OIT that was noted above, this biologic and its analog TNX-901 have been demonstrated to have considerable potential as monotherapy for the treatment of food allergy.⁶⁶⁻⁶⁸ In the study of TNX-901 by Leung et al,⁶⁶ 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 mg to 2805 mg of peanut flour. Savage et al³² 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 to 8. Of further note in this regard, Genentech recently announced that the US FDA has granted Breakthrough Therapy Designation for omalizumab for the prevention of severe allergic reactions following accidental exposure to 1 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.⁶⁹⁻⁷²

In addition to intervening directly upon IgE, a number of other pathways important in food allergy are being explored as potential targets for therapy. In particular, IL-33 is a cytokine that acts upstream of IgE and mediates B-class switching to IgE. In a phase 1 study of healthy volunteers, ANB020, a monoclonal anti-IL-33 antibody, demonstrated that a single dose was sufficient to suppress IL-33 function for approximately 3 months after dosing.⁷³ ANB020 is being further evaluated in a phase 2 placebo-controlled trial that is designed to determine safety and effects on biomarkers and oral peanut challenges in adult patients with peanut allergy (clinicaltrials.gov; NCT02920021).

There is great interest in studying other biologics that target other key molecules known to be involved in food allergy, many of which have now been approved for the treatment of other allergic diseases. We expect to see data on many of these products for the treatment of food allergy in the coming years, potentially including anti-IL-5 (mepolizumab and reslizumab) and anti-IL-5R (benralizumab); anti-IL4ra (dupilumab); QAX576, an anti-IL-13 antibody; tezepelumab (AMG 157/MEDI-9929), an anti-thymic stromal lymphopoietin antibody; and MEDI-528, an anti-IL-9 antibody. Of these, dupilumab is currently being studied in phase 2 as an adjunct to subcutaneous grass immunotherapy (clinicaltrials.gov; NCT03558997) and a program to also study it as an adjunct to peanut OIT has been publicly announced.

Adjuvant-enhanced SLIT

Although conventional peanut SLIT as described above is no longer being studied widely, the novel agent SAR439794 (clinicaltrials.gov; NCT03463135) is in early-stage development. This is a PE adjuvanted with Glucopyranosyl Lipid A (GLA). A phase 1, randomized, double-blind, placebo-controlled study of adolescents and adults with peanut allergy is underway, with 3 treatment arms comparing active PE/active GLA, active PE/placebo GLA, and placebo PE/placebo GLA. The goals of this study are to assess the safety, tolerability, pharmacodynamics, and immunogenicity of daily SLIT over a 12-week treatment period.

NEW RESEARCH QUESTIONS AND PRIORITIES

We anticipate that beginning in 2019, the widespread translation of new treatments into routine clinical practice will revolutionize the care of individual patients and the systems in which they receive care. Never before have new FDA-approved interventions been implemented at scale for food allergy, which will usher in the first transition from the T2 phase of translational research (large-scale clinical trials) to the T3

(implementation into real-world practice) and T4 (population-based health) phases, a transition that will stimulate entirely new areas for research (Table II). The expansion of the treatment-exposed population beyond the constraints of a clinical trial will enhance the clinical relevance of the observations and provide statistical power.

However, to pursue these objectives, it will be imperative to build new research infrastructure. Most importantly, a unified framework must be developed to establish what are the key clinical outcomes in the real world and to ensure that they are being measured and recorded correctly with data standards. The development of this clinical and health services research framework will require the input of a diverse group of stakeholders and ideally will proceed with a coordinated, organized effort to ensure alignment. Particular emphasis should be placed on identifying and measuring patient-centered outcome variables, using input from real patients and caregivers wherever possible. Once such a framework is developed, robust surveillance systems will be needed to record data from real-world patients under treatment. Ideally these surveillance systems will be networked, cross-platform, and easy-to-use. They should be nested within electronic health records and make use of in-stream data collection occurring during the provision of routine clinical care. Biorepositories, although difficult to establish and maintain, could significantly accelerate discovery. Once built, these systems will facilitate new kinds of T3/T4 research that until now have been exceedingly difficult or impossible to conduct in extensive numbers of participants and/or over prolonged periods.

SUMMARY/CONCLUSIONS

It now seems likely that 1 or more emerging therapies with an indication for the treatment of peanut allergy will soon be approved by the FDA and potentially other regulatory agencies for the first time. However, neither of the candidate treatments is curative, and real-world questions about safety and effectiveness remain. In parallel with these late-stage development programs, a deep pipeline of earlier-stage approaches is emerging, while at the same time OIT using commercially available food products is proliferating in the United States, despite current consensus guidelines discouraging it. The degree to which any of these treatments will protect patients in the real world and improve the psychosocial burdens of peanut allergy remain poorly understood. Meanwhile, strict allergen avoidance without an interventional treatment remains a viable alternative for some patients, and even for those receiving therapy, concurrent allergen avoidance will be required. Therefore, although we are optimistic about the future of the peanut allergy landscape, the availability of multiple management options, none of which are optimal, and substantial remaining knowledge gaps may increase complexity for patients and providers in the short-term. Successfully navigating this landscape will require not only a thorough discussion of patient and caregiver goals relative to the expected outcomes, AEs, and burdens of therapy, but also more studies using large, real-world populations to answer critical unknowns about long-term benefit/risk, adherence, and comparative effectiveness. Finally, we are excited about the potential of new treatments in the pipeline, but there remains a great need to harmonize clinical trial end points and data reporting conventions, and prioritize the development of appropriately patient-centered outcome measures, as has been

done in other areas. This approach will lead to a future where patients, caregivers, and providers can participate in informed, shared decision making in selecting a treatment that will ultimately improve that patient's life.

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