



Oral and Sublingual Immunotherapy for Treatment of IgE-Mediated Food Allergy

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Abstract

Development of active therapies for IgE-mediated food allergy is a critical action step toward alleviating the adverse medical, psychosocial, and economic burdens on affected patients and families. Significant progress has been observed specifically in the application of single-allergen oral and sublingual immunotherapy for treatment of IgE-mediated food allergy, with emphasis on milk, egg, and peanut as the primary allergens. Oral immunotherapy (OIT) has demonstrated efficacy in promoting immunomodulatory effects that lead to the clinical outcome of desensitization, defined as reduced reactivity while on active OIT, in the majority of treated individuals; however, achievement of sustained unresponsiveness following cessation of therapy has been observed in a smaller subset of treated subjects. The potential therapeutic benefits of OIT must be carefully considered in light of the significant potential for adverse events ranging from self-limited or easily treated oropharyngeal, respiratory or gastrointestinal symptoms, to persistent abdominal complaints that lead to cessation of therapy in an estimated 10–15% of treated individuals. To date, the majority of studies have focused on single-allergen OIT approaches; however, multi-allergen OIT has shown promise in initial trials and is the subject of ongoing investigation to address the complex needs of multi-food allergic individuals. Sublingual immunotherapy (SLIT) has been utilized for the treatment of food allergy and pollen-food allergy syndrome, demonstrating moderate efficacy, a favorable safety profile and variable tolerability, with oropharyngeal symptoms most commonly observed. Although studies directly comparing OIT and SLIT are limited, in general, the favorable safety profile associated with SLIT comes at the expense of reduced efficacy, while the more robust clinical effects observed with OIT come at the risk of potentially intolerable, treatment-limiting side effects. Future investigation to address specific knowledge gaps including optimal dose, duration, age of initiation, maintenance schedule, mechanisms, predictors of risk and therapeutic response will be important to maximize efficacy, minimize risk and develop personalized, effective approaches to targeting food allergy.

Keywords Food allergy · Specific IgE · Desensitization · Sustained unresponsiveness · Oral tolerance · Management · IgE-mediated food allergy · Oral food challenges · Oral immunotherapy · Sublingual immunotherapy

Introduction

Development of therapeutic strategies targeting IgE-mediated food allergy is critical to address the adverse impacts of this complex, increasingly prevalent disorder on affected individuals and families [1]. Indeed, the two primary long-term goals identified in the pivotal National Academies of Sciences, Engineering, and Medicine (NASEM) report titled “Finding

a Path to Safety in Food Allergy: Assessment of the Global Burden, Causes, Prevention, Management and Public Policy” are to (1) develop safe and effective therapies and (2) prevent onset of food allergies [2]. The present standard of care for food allergy includes strict dietary elimination of the implicated food allergen(s), nutritional support and education, ongoing clinical follow-up, and development of emergency action plans with immediate access to injectable epinephrine in case of accidental allergen exposure or ingestion [1]. However, this approach is confounded by difficulties associated with vigilant adherence to food elimination diets, ongoing risks of accidental ingestions, exposure to hidden food ingredients/cross-contamination, and the risk of severe or even fatal food reactions, requiring intensive, ongoing education, and support for optimal management [3, 4]. Significant progress toward active

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interventions for food allergy has been realized over the past two decades as licensed single-allergen therapies for peanut allergy are currently on the horizon [5]. However, despite significant advances, immunotherapeutic approaches to food allergy such as oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) remain experimental, and addressing significant gaps in knowledge such as optimal dose, duration, age of initiation, predictors of response, and improved understanding of immune mechanisms underlying therapeutic outcomes is vital to continue to advance the field. This review highlights the current state of the art in mucosal immunotherapy for food allergy through evaluating the safety and efficacy of single- and multi-allergen specific OIT as well as SLIT for the treatment of IgE-mediated food allergy.

Therapeutic Outcomes and Mechanisms of Immunotherapy

A detailed review of the complex mucosal immune responses underlying IgE mediated food allergy is beyond the mandate and scope of this article. However, a recent review by Tordesillas et al. elegantly summarized the current understanding of the innate, adaptive and effector cell and tissue responses involved counter-regulation between pro-allergic and tolerogenic immune responses involved in food allergy and effective immunotherapy [6]. At the most basic level, food allergy results from aberrant development of mucosal tolerance to food allergens; therefore, most immunotherapeutic approaches to date have capitalized on modulating the immune response through mucosally targeted interventions such as OIT and SLIT in an allergen-specific manner. The postulated mechanism of action of OIT and SLIT involves activation of gastrointestinal dendritic cells or Langerhans cells in the oral mucosa to promote tolerogenic downstream immunoregulatory mechanisms that polarize adaptive and effector responses [7, 8].

Therapeutic outcomes following food allergen immunotherapy include desensitization and sustained unresponsiveness [4, 8] (Fig. 1). Desensitization is defined as elimination of clinical reactivity with an increased reaction threshold to a food allergen while on active therapy, an outcome which is achieved after only months on therapy and offers potential protection from accidental ingestions. Sustained unresponsiveness is defined as elimination of clinical reactivity to a food allergen after a specified period of cessation of therapy and appears to require some degree of continued allergen exposure to preserve the nonresponsive state. Development of sustained unresponsiveness takes years of therapy and has been achieved in only a subset of individuals [9, 10]. The concept of “oral tolerance” indicates a specific immune response that does not result in clinical reactivity after allergen consumption, typically reserved to define naturally occurring tolerance that occurs during early life food exposures [11].

Development of clinical and immunologic tolerance following experimental immunotherapy has not been observed in OIT or SLIT trials to date, and this finding has important implications for clinical outcomes and long-term management strategies.

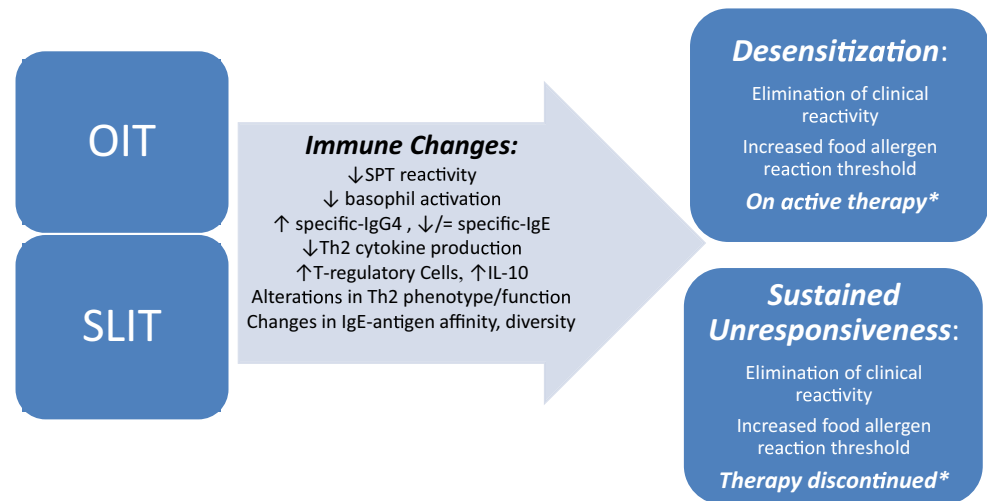
While the mechanisms associated with beneficial clinical outcomes following immunotherapy are a topic of ongoing investigation, the typical parameters associated with positive responses in OIT and SLIT trials to date include increased allergen-specific IgG4, decreased skin prick test (SPT) and basophil reactivity, reduced T-helper type 2 (Th2) cytokine responses, and induction of regulatory T-cells (Tregs) [10, 12–15]. The time course of the early immunomodulatory changes observed during the first few months of OIT specifically includes decreased basophil and mast cell reactivity observed in reduced SPT wheal size and basophil activation testing (BAT), along with increased allergen-specific IgG4 levels. Food-specific IgE levels typically demonstrate an early increase during the initial months of OIT, followed by decreased sIgE levels, which in one study were associated with alterations in IgE-antigen binding affinity and epitope diversity [16]. Transition from a Th2 predominant cytokine signature to a Th1-associated pattern has been observed after 6–12 months of therapy [12]. Later OIT effects include induction of antigen specific Tregs [14, 17]. Investigators have observed that OIT- and SLIT-induced immunologic changes may be temporary, even while receiving maintenance treatment, highlighting interindividual variability in immune suppression and clinical response [14].

Alternate approaches evaluating component resolved analysis during egg OIT identified predictors associated with sustained unresponsiveness including egg white- specific IgG4, IgA, and IgA2, with lower pretreatment egg white- and ovomucoid-specific IgE associated with development of sustained unresponsiveness [18]. Additionally, investigators have identified phenotypically and functionally distinct Th2 subsets as potential predictors of therapeutic response to OIT [19, 20]. Development of an “anergic” CD4+ Th2 phenotype and elimination of a pathogenic Th2A subset specific to atopic individuals were associated with beneficial outcomes during OIT in these two studies. Enhanced understanding of the immunoregulatory mechanisms during effective immunotherapy is important for development of biomarkers that might eventually predict therapeutic outcomes.

Oral Immunotherapy (OIT)

OIT is an experimental immunomodulatory approach with the largest body of evidence among emerging therapies for food allergy. During OIT, food allergen(s) are combined with a vehicle food and consumed in incrementally increasing doses over a specified time interval with a goal of inducing clinically relevant immunomodulation leading to clinical outcomes of

Fig. 1 Outcomes of immunotherapeutic approaches for food allergy. OIT and SLIT induce varying degrees of immunomodulation to induce clinically relevant outcomes of desensitization and sustained unresponsiveness



*antigen exposure required to maintain effects

either desensitization or sustained unresponsiveness [10, 13, 21–25]. Participants are carefully selected for enrollment in OIT studies based typically on a combination of clinical history, skin prick test (SPT) wheal size, specific IgE parameters, and baseline oral food challenges (OFCs) to confirm clinical reactivity. (Figure 2) Specific allergen and vehicle forms have varied in different studies, with some investigators utilizing commercially available food products (e.g., milk in typical liquid form, peanut flour) and while others have used specially prepared products such as dehydrated egg powder mixed with vehicle. Although OIT employs the use of food proteins, as research protocols have advanced and are utilized for therapeutic indications, the US Food and Drug Administration (FDA) has required investigators to obtain investigational new drug (IND) approval to assure standardization regarding investigational product safety and identification and quantification of allergenic proteins [5]. Indeed, important recently published work in peanut OIT analyzed the specific allergen profiles of peanut-containing foods, diagnostic reagents and therapeutic allergen-based products [26, 27]. Although all major peanut allergens were present in the preparations, there was significant variability in the allergen and peanut component composition, highlighting the importance of well-characterized and standardized products, particularly for treatment approaches.

Although different protocols have been utilized, a typical OIT protocol utilizes a combination of different treatment phases including initial dose escalation (IDE) typically performed as a modified rush-immunotherapy approach during a 1–2-day period under close clinical observation, followed by daily home dosing buildup phase with observed weekly to bi-weekly dose increases performed at the clinical center typically over a period of months, to achieve a target maintenance dose (range 300 to 4000 mg in published trials) which is consumed for a prespecified duration [4, 5, 8] (Fig. 3).

After completion of the maintenance dosing period, oral food challenges are typically performed while on therapy to assess desensitization; depending on the specific protocol, individuals who pass the desensitization challenge may then go on to cease daily therapy for a period of time and return for a “sustained unresponsiveness challenge” to assess clinical reactivity while off of therapy. From long-term studies, it appears that ongoing allergen exposure is required for maintenance of desensitization and sustained unresponsiveness and protective effects can diminish over time [23, 28].

OIT trials to date have primarily utilized single-allergen preparations in patients with allergies to multiple different foods, with the majority focused on peanut [10, 12, 21, 22, 25, 29, 30], milk [24, 28, 31–35], and egg [9, 13, 36, 37] although treatment of food allergy due to other allergens is the subject of ongoing investigation [38]. In addition, approaches using multi-allergen OIT for the simultaneous treatment of multiple food allergies is an area of significant interest and investigation. An initial study of multi-allergen OIT demonstrated comparable safety and efficacy between single-allergen peanut OIT and multi-allergen OIT with up to five foods [39].

Systematic reviews and meta-analyses have evaluated the collective evidence regarding OIT [40–43]. Analyses focused specifically on milk OIT concluded that it is an effective approach; however, the need for larger studies to enhance the quality of the evidence and the importance of balancing the therapeutic benefits with the potential for frequent and serious adverse side effects must be carefully considered [40, 41]. In a systematic review and meta-analysis of orally administered immunotherapy for treatment of allergy to several different food allergens, investigators summarized the available evidence from 18 randomized controlled trials (RCTs) and 3 controlled clinical trials, concluding that there is strong evidence that treatment promotes immunomodulatory changes

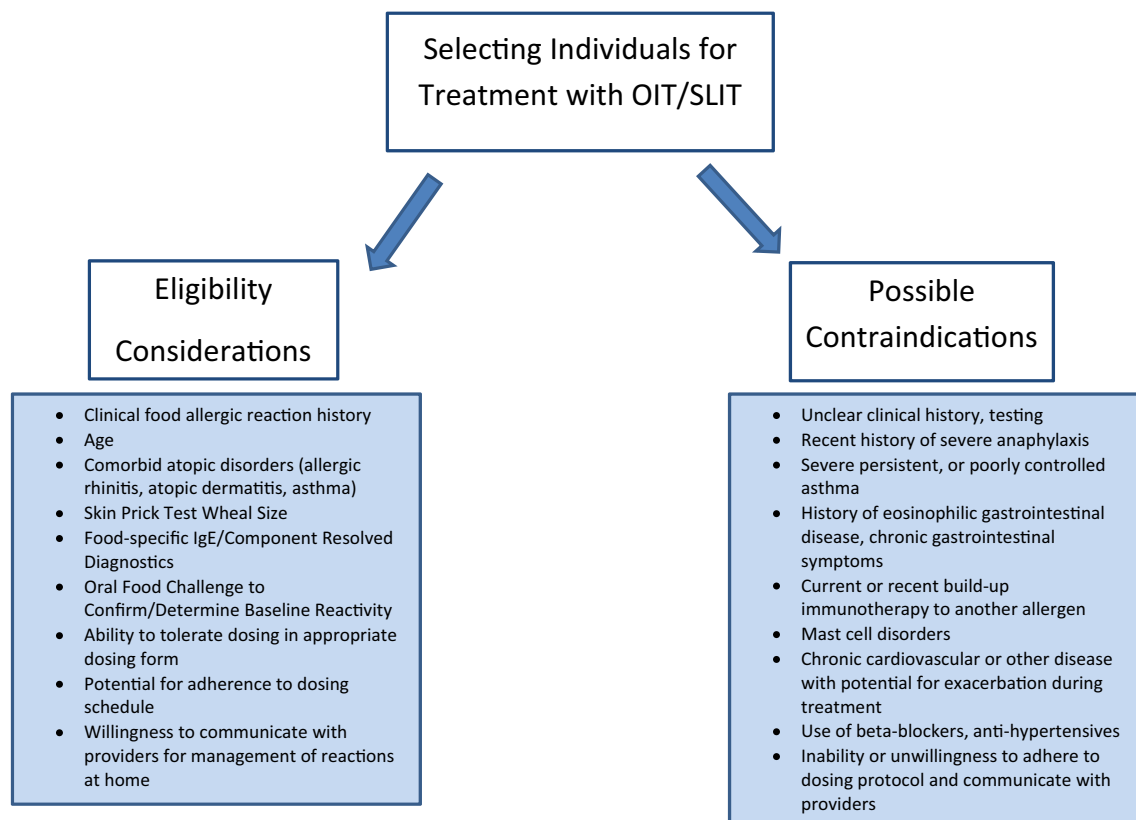


Fig. 2 Selection of appropriate individuals for treatment is critical for safe and effective use of immunotherapeutic approaches to food allergy

that promote desensitization to a range of foods; however, longer-term safety, efficacy, and cost-effectiveness data is needed and the approach remains experimental [42]. In a more

recent analysis which included 25 RCTs and 6 nonrandomized studies (25 OIT, 5 SLIT, 1 EPIT) again supported the effectiveness of therapy to increase the threshold of reactivity to a

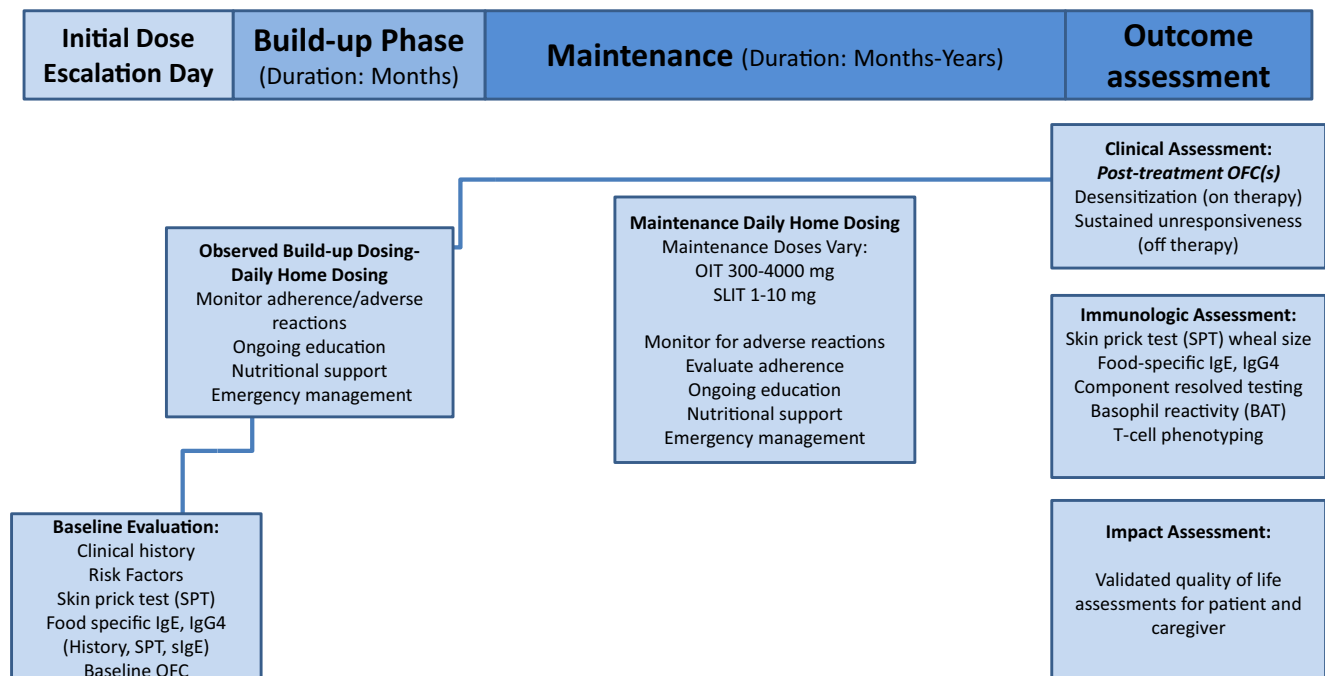


Fig. 3 OIT and SLIT protocols typically combine multiple phases of therapy including initial dose escalation, dose buildup phase, maintenance home dosing, and outcome assessment. The dose and duration varies depending on specific protocols and interventions

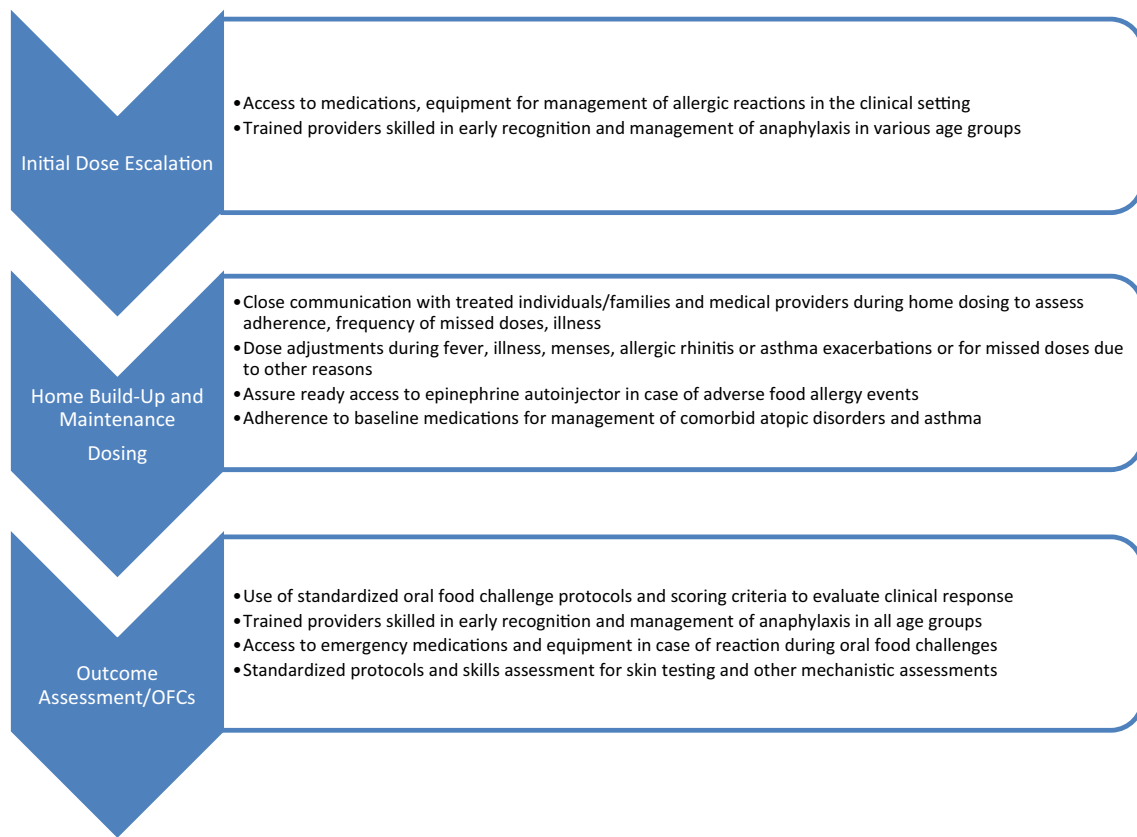


Fig. 4 Safety considerations throughout immunotherapy protocols, including the importance of assessing adherence to therapy and dose adjustments during episodes which can potentially lower an individual's reaction threshold to dosing

variety of foods while on therapy and after discontinuation of therapy, recognizing a modest increased risk of serious systemic adverse reactions and substantial increase in minor local adverse reactions and indicating the need for more data regarding long-term outcomes, impact on quality of life, cost-effectiveness, and adult treatment outcomes [43].

Safety of OIT

Despite some evidence of potential benefit, treatment of food allergy using subcutaneous immunotherapy (SCIT) is impractical and unsafe for broad clinical application due to an unacceptably high rate of severe systemic reactions (44, 45). Although OIT has resulted in the highest rates of desensitization and sustained unresponsiveness of all mucosal immunotherapeutic approaches evaluated to date, the potential risk of OIT-related serious adverse events, such as anaphylaxis, eosinophilic esophagitis, and dose-limiting gastrointestinal side effects must be carefully considered [4, 5, 46, 47]. The most commonly observed symptoms are mild-to-moderate, typically involving oropharyngeal pruritus or transient abdominal pain that is either self-limited or easily treated with antihistamines [13, 22, 24, 25, 46]. However, an estimated 10–15% of OIT-treated subjects experience intolerable abdominal symptoms that preclude continuation of therapy [48]. Overall

withdrawal rates from OIT trials due to adverse effects are estimated between 10 and 20%, with rates as high as 36% observed; these adverse events represent a barrier to broad implementation of OIT in clinical practice [5]. Eosinophilic esophagitis has been reported as a complicating disorder in a subset of OIT-treated individuals, and more work is critical to understand the relationship between OIT and development of EoE [49, 50]. Because individuals receive multiple OIT doses over an extended period of time the safety risk for any given patient can be substantial. Indeed, in a study of milk OIT in 24–36-month-old children, investigators in Spain reported effective desensitization, but side effects were common in this young cohort, with 24/30 (80%) overall reporting a reaction (14/30 [47%] moderate, 10/30 [33%] mild) with urticaria, angioedema, or cough most commonly observed [51]. Recent work from Virkud and colleagues provided important insight into risk factors predicting side effects associated with peanut OIT by evaluating adverse events (AEs) in 104 participants in 3 peanut OIT trials [52]. The authors reported that 80% of participants experienced AEs with 42% having systemic symptoms and 49% having gastrointestinal symptoms; 20% dropped during the study, half due to gastrointestinal symptoms. Asthma and allergic rhinitis predicted systemic symptoms and higher skin prick test wheal size was predictive of gastrointestinal AEs.

A detailed assessment examining the safety of peanut OIT throughout all phases of treatment was published in tandem with the first open-label peanut OIT trial [12, 46]. Adverse reactions were most frequently observed during the initial dose escalation phase with the majority of subjects requiring some form of treatment. Although the reported frequency of adverse reactions was decreased during the buildup and home dosing phases of the study, two subjects in this cohort required epinephrine for treatment of adverse reactions during home dosing. Further examination of adverse reactions during home dosing identified five scenarios associated with increased risk of reaction including concurrent illness, physical exertion following dose administration, dosing during menses, poorly controlled asthma and timing of dosing following food ingestion [53]. In other trials, severe reactions requiring treatment with epinephrine and beta-agonists have most commonly been observed during dose escalation but were also observed after reaching maintenance dosing [24, 29, 31, 34, 51]. In a study of peanut OIT performed in clinical practice settings, Wasserman et al. reported outcomes in 352 treated patients who received a total of 240, 351 doses of peanut, peanut butter, or peanut flour with 298 (85%) achieving target maintenance dose (85%). Severe reactions requiring the use of epinephrine occurred in 95 patients, and 3 patients required 2 doses of epinephrine [54]. Unsettlingly, severe reactions can be unpredictable and occur with previously tolerated doses and are often, but not always, associated with modifiers such as infection, exercise, or multi-allergen exposure [21, 24, 33, 46]. Potential strategies to enhance safety throughout immunotherapy protocols are listed in Fig. 4.

Efficacy of OIT

In different protocols targeting primarily milk, egg, and peanut allergy, OIT has been shown to induce clinically relevant desensitization in an estimated 36–100% of treated individuals, while sustained unresponsiveness, when assessed, was observed in approximately 28–75%; development of long-term tolerance without ongoing antigen exposure remains an elusive goal [10, 12, 13, 17, 22, 25, 28, 55, 56]. In a recently published meta-analysis, the authors concluded that the evidence for desensitization following OIT is strong; however, further evidence regarding longer-term safety and efficacy endpoints, dosing in adults, cost-effectiveness, and impact on quality of life (QoL) is needed [43]. Recent work indicated that the impact of oral immunotherapy on QoL was variable, with subject exhibiting impaired QoL at baseline improved significantly despite the burdensome demands of therapy, whereas some patients with acceptable QoL at baseline had deterioration due to the demands associated with OIT [57].

Efficacy: Single-Allergen Peanut OIT Trials

Initial case reports of peanut OIT provided proof-of-concept for effective oral desensitization in peanut allergic individuals [58, 59]. Subsequently, the first open-label prospective cohort study of peanut OIT in the USA established both the clinical efficacy of peanut OIT for induction of immunoregulatory changes that promote desensitization as well as the relative safety of OIT [12]. In this trial, 29 children completed 36 months of peanut OIT with a maintenance dose of 1800 mg with 27/29 (93%) ingesting 3.9 g of peanut protein during OFC, supporting the role of OIT in effective clinical desensitization. Titrated SPTs and basophil reactivity significantly declined by 6 months. Treated patients demonstrated initial increases in peanut-specific IgE which subsequently decreased by 12 and 18 months on therapy, whereas peanut-specific IgG4 increased significantly throughout the study. Additionally, a 1.5-fold increase in FOXP3+ Tregs was noted in peanut stimulated cells at 6 and 12 months on therapy, with contraction of the population thereafter. Blumchen and colleagues utilized a peanut OIT protocol that included a 7-day rush OIT treatment phase, followed by a long-term buildup protocol with bi-weekly dose increases up to 0.5 g of peanut protein, and a subsequent 8-week maintenance phase [22]. Twenty-three subjects underwent the rush OIT protocol, with 22/23 continuing the maintenance protocol. The median threshold dose eliciting symptoms after rush OIT was 0.15 g, whereas, after long-term treatment, the median tolerated dose was 1 g. Immunologic changes while on OIT included significant increases in peanut specific IgG4, and significant decreases in Th2 cytokine production by PBMCs.

The first randomized, double-blind, placebo-controlled, multi-center trial of peanut OIT enrolled 28 pediatric subjects (age 1–16 years) randomized to peanut OIT or placebo; three peanut OIT subjects withdrew due to allergic side effects [25]. During the 1-year double-blind, placebo-controlled food challenge, all peanut OIT subjects ($n = 16$) ingested the maximum cumulative dose of 5000 mg (~20 peanuts), whereas placebo subjects ($n = 9$) ingested a median cumulative dose of 280 mg (range, 0–1900 mg). The peanut OIT group demonstrated significant reductions in SPT wheal size, Th2 cytokine production, along with significant increases in peanut-specific IgG4 and Foxp3hi expressing Tregs. In an open-label, prospective study of peanut OIT in 22 children receiving a maintenance dose of 800 mg for 32 weeks, investigators observed 14/22 (64%) tolerated a 6.6 g OFC at the end of treatment (86% tolerated updosing) [60]. Three years later, the same investigators performed a randomized controlled trial of peanut OIT with a maintenance dose of 800 mg, reporting desensitization in 62% of active peanut OIT group [21].

While initial trials provided foundational evidence for desensitization and relative safety of peanut OIT, the first report evaluating sustained unresponsiveness as a primary outcome

was published in 2014 [10]. After up to 5 years of OIT in children aged 1–16 years (4000 mg maintenance dose), 12/24 (50%) of subjects with evaluable outcomes passed a 5 g sustained unresponsiveness OFC performed 4 weeks after cessation of OIT. Smaller SPT wheal size and lower specific IgE levels for peanut, Arah1, Arah2, and lower peanut-specific IgE/total IgE ratios at baseline and at the OFC were predictive of successful outcome. Recent work highlights the potential window of opportunity for early intervention to maximize the therapeutic efficacy of OIT in young children. Vickery et al. reported the safety, efficacy, and feasibility of early peanut OIT in 37 children age 9–36 months randomized to either low dose 300 mg or high dose 3000 mg daily maintenance doses [61]. The primary endpoint, sustained unresponsiveness 4 weeks after discontinuation of OIT following a median 29 months of treatment, was achieved in 29 of 37 (78%) in the intent-to-treat analysis (300-mg arm, 17 of 20 [85%]; 3000 mg arm, 12 of 17 [71%]). In the per-protocol analysis, 29 of 32 (91%) achieved the primary sustained responsiveness endpoint. Significantly decreased peanut specific IgE levels were observed in early OIT-treated children. Allergic side effects were common, but all were mild to moderate. Although further study is needed, this foundational study supports both the value of early OIT to enhance the response to therapy, as well as the efficacy of lower maintenance doses to achieve similar therapeutic response.

In a randomized, double-blind, placebo-controlled trial of probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 plus peanut OIT in peanut allergic children 1–10 years stratified by age (≤ 5 and > 5 years) and peanut SPT wheal size (≤ 10 and > 10 mm), subjects received either probiotic peanut OIT (PPOIT) or placebo treatment and investigators reported sustained unresponsiveness (2–5 weeks after discontinuation) in 82.1% receiving PPOIT and 3.6% receiving placebo. Desensitization was observed in 89.7% receiving PPOIT and 7.1% placebo ($P < .001$). Significant decreases in peanut SPT and peanut-specific IgE levels and increased peanut-specific IgG4 levels were observed in the active treatment group. Although this approach was associated with clinical efficacy and immunomodulation, the relative contributions of probiotics vs. OIT could not be evaluated in this study design and further study is needed [62].

Recently published work from Hourihane and colleagues reported their experience with a home-based peanut immunotherapy clinical treatment approach (without IRB protocol) in carefully selected pediatric patients with a clinical phenotype of tolerance to low-doses and mild reactions to higher doses [63]. Sixteen children (ages 6–13 years) were treated clinically with weekly home buildup doses of 1 to 4 peanuts consumed 3–7 days/week through 6 months of therapy followed by open OFC. Of the 10 individuals with evaluable OFC data, 63% were desensitized at the 6-month OFC and 50% achieved sustained unresponsiveness (after a 6-week period of OIT

cessation) to a dose of 8 peanuts (~2400 mg peanut). Importantly, no safety events were reported. While safety is always the primary concern, this thought-provoking work highlights the important need for future investigation of different food allergy clinical phenotypes and ultimately disease endotypes (phenotypic subclasses associated with specific disease mechanisms) to develop personalized approaches to management. The contemporary progress toward development of precision medicine strategies in asthma, drug allergy, food allergy, and anaphylaxis is explored in a PRACTALL consensus document [64]; while significant further investigation is needed to apply these strategies in food allergy, these considerations have important implications for the refinement and standardization of clinical evaluation tools and the design of management approaches to mitigate the adverse effects of food allergy, improve quality of life, and reduce the pervasive anxiety that often comes with a diagnosis of food allergy.

Efficacy: Single-Allergen Egg OIT Trials

Initial reports of successful desensitization using egg OIT provided important proof of concept for therapeutic efficacy [65, 66]. In an early pilot study, Buchanan et al. utilized an open-label egg OIT protocol to desensitize egg allergic children; in the seven subjects who completed the 24-month protocol, four passed a double-blind, placebo-controlled food challenge to 10 g of egg at the conclusion of the therapy, and all subjects tolerated significantly higher doses of egg protein than noted at entry into the study [36]. A subsequent report indicated that 2/21 subjects enrolled in this ongoing protocol were unable to achieve the maintenance egg protein dose due to frequent and unacceptable therapy-associated adverse reactions (67). In long-term follow-up study in this same cohort, higher individualized doses based on egg-white-specific IgE values (median 2400 mg) were continued for a median duration of 33 months, with all six subjects who completed the long-term protocol demonstrating sustained unresponsiveness following a 4-week period of OIT discontinuation [37]. Two randomized controlled trials comparing egg OIT with avoidance demonstrated complete or partial desensitization in 60–70% of treated subjects [55, 67]. Additional small randomized controlled trials reported desensitization rates as high as 80–90% in protocols using raw hen's egg OIT and including pediatric subjects with severe egg allergy, as well as two studies using rush oral immunotherapy protocols that resulted in desensitization in as little as 5 days [68–71].

The results of the first multi-center, randomized, double-blind, placebo-controlled trial of egg OIT in children were published in 2012 [13]. In this trial, 55 subjects aged 5–11 years received a maintenance dose of 2 g of egg protein with DBPCFC performed after 10 and 22 months of therapy. After 10 months of therapy, 55% of the individuals receiving active egg OIT were desensitized in contrast to none of the

placebo treated subjects. After receiving 22 months of OIT, 30/40 (75%) were desensitized; however, only 11 subjects (28%) demonstrated sustained unresponsiveness when challenged after 6–8 weeks off egg OIT. In a long-term egg OIT trial in children and adolescents, COFAR investigators reported progressive benefit of continued therapy with 50% of participants achieving SU by year 4 compared to only 28% by year 2 [72]. In addition, 100% of subjects achieving SU were able to consume both baked and concentrated egg products ad libitum during a 4-year follow-up period.

Efficacy: Single-Allergen Milk OIT Trials

In addition to their work with egg OIT discussed above, Patriarca and colleagues also performed pioneering work with milk OIT, reporting desensitization rates ranging from 65.5 to 100% [65, 66]. Meglio and colleagues reported both complete and partial desensitization in a pilot study in 21 children treated with 6 months of milk OIT, with 15/21 (72%) tolerating the goal daily dose of 200 ml, and an additional 3/21 (14%) tolerating lower daily doses [73]. Even partial desensitization dramatically reduced the risk of severe reactions after unintentional ingestion of small quantities of cow's milk. Four years after open-label milk OIT, this same group observed that 14/20 (70%) maintained partial/full desensitization associated with significant reductions in SPT reactivity and milk-specific IgE levels [74]. Additional reports in nonrandomized studies supported the overall efficacy of milk OIT to induce desensitization [75–77].

In 2005, investigators reported findings in three patients enrolled in a randomized, placebo-controlled study of oral tolerance induction therapy for cow's milk or egg allergy [78]. Home daily dosing was conducted until patients achieved tolerance to 250 mL milk or 4.5 g egg protein (range 37 to 52 weeks). Daily dosing was followed by an elimination diet for 2 months and then a double blind, placebo controlled food challenge. Of the two patients who underwent the final food challenge, both experienced moderate systemic allergic reactions, similar to their symptoms prior to therapy, suggesting transient therapeutic effects. In the first large randomized controlled trial of milk OIT, investigators utilized this same approach and reported findings in 45 subjects, observing that 9 of 25 children (36%) in the treatment group, versus 7 of 20 (35%) in the control, standard avoidance arm exhibited clinical nonresponsiveness; these similar rates in the treatment vs. standard avoidance groups suggest that therapy may not have an enhanced benefit over natural tolerance acquisition observed in the standard avoidance arm. However, 7 children in the treatment group were considered either partial or full responders when regularly consuming milk protein, boosting the rate of any response to 64%, and potentially offering protection from accidental exposures [79].

In a subsequent study of milk oral immunotherapy for children with history of severe allergic reactions and high milk-specific IgE levels, 60 children (age > 5 years) were randomized to milk OIT or elimination diet [80]. After 1 year, 36% of children in the treatment group were completely tolerant to milk (at least 150 mL daily), 54% could tolerate 5 to 150 mL of milk daily, and 10% did not complete the protocol because of persistent respiratory or abdominal complaints. In contrast, in the avoidance group, all 30 patients failed a double-blind, placebo-controlled food challenge after 1 year. Half of patients in the treatment group had significant decreases in IgE specific to cow's milk at 6 and 12 months. In the control group, milk-specific IgE levels remained essentially unchanged, and none of the children spontaneously acquired tolerance. Symptoms associated with treatment included oral pruritus, urticaria, abdominal pain with or without vomiting, rhinoconjunctivitis, mild laryngospasm, and mild bronchospasm which were treated with either oral steroids, nebulized epinephrine, or intramuscular epinephrine. Further investigation of rush oral immunotherapy for persistent cow's milk allergy reported findings in 9 children, 6/9 reached the maximal dose of 120 ml of milk with only mild to moderate symptoms, which did not require emergency medications as in the Longo study [81].

In a randomized, placebo-controlled cow's milk OIT trial investigators observed increased median milk threshold dose during oral food challenge performed after 13 weeks of 500 mg maintenance dosing (40 → 5140 mg OIT vs. 40 → 40 mg placebo) in children treated with milk OIT-treated children aged 6–17 years ($n = 12$) compared with placebo ($n = 7$) [82]. Milk-specific IgG4 was significantly increased in the OIT treated group, although no significant differences in IgE level between groups were observed. The most common reactions included oral pruritus and abdominal pain, with all patients on active therapy experiencing at least one adverse reaction; however, 90% of reactions were transient and required no treatment. This cohort was followed long-term during an open-label portion of the study to evaluate the continued safety of milk OIT and the subjects' ability to tolerate gradual home dose escalation [33]. Six of 13 patients undergoing follow-up food challenge tolerated the maximum cumulative dose of 16,000 mg (16 oz) of cow's milk protein without any adverse reaction. The other seven participants tolerated doses ranging from 3000 to 16,000 mg, with associated clinical symptoms including oral pruritus, abdominal pain, sneezing, cough, and urticaria. Relevant decreases in end-point titration SPT and milk specific IgE and significant increases in milk-specific IgG4 were detected following OIT. Pajno and colleagues published findings from a randomized, placebo-controlled trial of 15 children (age 4–19 years) of milk OIT in an 18-week protocol with a 200 ml maintenance dose that indicated that 67% tolerated 200 ml of cow's milk; this same group of investigators subsequently reported comparable

efficacy with daily or twice weekly maintenance to maintain desensitization [34, 83]. Evaluation of the optimal dosing regimens to maintain beneficial therapeutic effects of OIT while optimizing long-term safety and tolerability, and minimizing “dosing fatigue” will be important to inform the long-term approach to maintenance OIT. While it appears that continued antigen exposure is important, this work highlights that daily therapy may not be necessary to maintain desensitization, which has important therapeutic implications.

Investigators in Spain reported outcomes at 1 year in a randomized, placebo-controlled trial in children age 24–36 months treated with milk OIT (200 ml maintenance dose, $n = 30$) or standard milk avoidance ($n = 30$) [51]. After 1 year, 90% of the milk OIT-treated children were desensitized vs. 23% of the children in the avoidance group; clinical effects were associated with decreased SPT reactivity and milk- and casein-specific IgE from baseline in the milk OIT group. Side effects were common during OIT in this cohort, as 24/30 (80%) developed a reaction (14/30 [47%] moderate, 10/30 [33%] mild) with urticaria, angioedema, or cough most commonly reported..

Long-term follow-up of milk OIT indicated that even in subjects who had been tolerating significant amounts of milk at study completion, only 31% continued to tolerate uncooked milk without symptoms, 22% limited milk consumption due to allergic symptoms, 6% consumed only trace amounts of milk, and 16% avoided milk completely [23]. These findings have important implications for the long-term management of food allergy and will inform the next-generation design of safe, effective, tolerable immunomodulatory therapies for food allergy.

Extensively Heated Foods as OIT

Heating of milk and egg disrupts conformational epitopes created by protein folding and reduces immune recognition. Approximately 70 to 80% of children allergic to milk and egg can safely ingest extensively heated egg and milk products [84, 85]. Ingestion of 1–3 servings of baked allergen products daily was associated with accelerated development of milk and egg tolerance when compared to age matched controls. Therapy with extensively heated foods has been associated with decreased immune activation and a shorter time to tolerance induction when compared to diet restriction alone. In subjects with IgE-mediated egg allergy who passed physician-supervised oral food challenges to extensively heated egg (e.g., muffin or waffle) and incorporated these foods into their diet, continued consumption of heated egg protein was associated with decreased skin test size, reduced egg-specific IgE levels, and increased IgG4 levels. Despite these benefits, determination of extensively heated egg or milk tolerance can still be problematic. Neither skin prick nor specific IgE testing accurately identify which patients can tolerate

extensively heated foods; thus, an oral food challenge is often required before these foods can be added to the diet. In a retrospective study, investigators reported the outcomes of 84 baked milk OFCs performed in a food allergy referral clinic, observing that 72% were baked milk tolerant, and 12% of all individuals challenged (42% of reactors) had mild anaphylaxis that responded to in office medications and did not require prolonged monitoring beyond the 2-h observation period [86]. Milk sIgE levels were higher in reactive patients, while SPT wheal size was similar in baked milk-tolerant and reactive subjects. To maximize safety and minimize risk, assessment of baked milk or egg tolerance requires supervised challenges in a clinical setting with an allergist who is skilled in the identification and management of food allergic reactions.

Multi-Allergen OIT

Because the burden of food allergy is particularly amplified in individuals allergic to multiple foods, increased interest and investigation in the safety and efficacy of combination multi-allergen oral immunotherapy is the subject of ongoing investigation. Published findings from a single-center phase I trial including 40 participants ($n = 15$ peanut mono-allergic, $n = 25$ peanut plus other food allergies) received either single-allergen peanut OIT (maximum daily maintenance dose 4000 mg) or multi-allergen OIT using up to five allergens (peanut, tree nuts, sesame, milk, egg, maximum maintenance dose 4000 mg per allergen, up to 20,000 mg cumulative for those on 5 allergen OIT). All but three study participants ($n = 2$ dropouts, $n = 1$ excluded due to atopic dermatitis flares) achieved a 10-fold increase in their reaction threshold; the median time to achieve this increased reaction threshold was 14 weeks shorter in the single-allergen peanut OIT group vs. the multi-allergen OIT group. Reaction rates per dose were not significantly different between groups receiving single- vs. multi-allergen OIT (3.3 vs. 3.7% multi-OIT vs. single-allergen peanut OIT). In both groups, reactions were generally mild; however, two severe reactions occurred in each group requiring treatment with epinephrine [39]. A second phase I study demonstrated successful multi-food desensitization following pretreatment with omalizumab with subsequent rush multi-allergen OIT to multiple foods was utilized [87]. The use of combination approaches including omalizumab is discussed further in another section of this journal. Multi-allergen OIT was shown to improve quality of life in caregivers of food-allergic pediatric subjects as assessed by the Caregiver HRQL and FAQL-PB questionnaires [88].

Sublingual Immunotherapy for Food Allergy

SLIT is an approach that involves sublingual delivery of a daily dose of food protein in liquid concentrate that is held in place for a couple minutes, then spit or swallowed. SLIT

involves the use of smaller doses than OIT, typically starting with microgram amounts, advancing incrementally over the course of months to maintenance doses in the 1–10 mg range which are generally continued for multiple years of therapy. Mechanistically, SLIT is thought to take advantage of tolerogenic antigen presenting cells in the oral mucosa, with further benefit thought to be derived from exposure to the food protein in the intact form before proteins are subjected to gastric digestion [89, 90]. SLIT promotes desensitization in most patients after 1 year of treatment and moderate immunologic changes; longer-term studies of sustained unresponsiveness are needed [91–95]. Investigators first reported the efficacy of SLIT for treatment of hazelnut allergy [94]. Following 8–12 weeks of therapy, 11 of the active hazelnut SLIT subjects reached the target dose, with 5 subjects able to successfully tolerate 20 g of hazelnut during oral food challenge without dose limiting symptoms (vs. 1/11 in placebo group). The mean tolerated dose increased from 2.3 to 11.6 g in the active SLIT group.

The first double-blind, placebo-controlled trial of peanut SLIT was published in 2011 [91]. Investigators randomized 18 pediatric subjects to peanut SLIT (target dose 2.5 mg) or placebo. All 11 peanut SLIT-treated subjects exhibited evidence of desensitization with median tolerated dose during post-SLIT OFC of 1710 mg; in comparison, placebo-treated subjects tolerated only median dose of 85 mg. Side effects were infrequent, mostly limited to oropharyngeal symptoms and in the majority of cases did not require significant intervention. A second double-blind, placebo-controlled trial of peanut SLIT included 40 adolescent and adult subjects randomized to peanut SLIT with target dose 1.4 mg or placebo [92]. A 5 g OFC was performed after 44 weeks of therapy; 14/20 in the active treatment group were considered responders (increase in median tolerated dose 3.5 to 496 mg) compared with 3/20 in the placebo-treated group. In a total of 10,855 doses administered during the first 44 weeks, 63% of doses were symptom free; if oropharyngeal symptoms were excluded, 95% of doses were symptom free. A 3-year long-term follow-up study reported similar observations regarding “modest level of desensitization” with favorable safety outcomes [93]. Interestingly, however, despite favorable safety profile, very few subjects in this adolescent/adult cohort continued therapy for the full 3 years. Dose-related symptoms after a year on therapy did not appear to be the primary cause of early study discontinuation; indeed, the most common reasons given for early withdrawal included “participant decision” or nonadherence. While the motivation for cessation of therapy was not formally assessed in this study, potential concerns identified included the difficulty of maintaining daily therapy, mild oral discomfort, lack of perceived robust response to

therapy, and lifestyle issues in the adolescent and adult subjects. Sustained unresponsiveness was observed in a very small subset of 4/37 subjects (10.8%). To better predict peanut SLIT outcomes, Burk and colleagues evaluated the ability of peanut components to predict response to peanut SLIT in a cohort of 33 children treated for 1 year and assessed by OFC, observing that lower baseline peanut, Ara h 2 and Ara h 3 specific IgE predicted successful desensitization [96].

In a recent SLIT study using recombinant allergen to treat birch-pollen-related apple allergy, investigators compared SLIT with recombinant major birch pollen allergen (rBet v 1) to SLIT with recombinant major apple allergy allergen (rMal d 1) [97]. Among 60 adults (ages 18–65 years) who received 4 months of SLIT, both extracts resulted in minor oropharyngeal symptoms, but only SLIT with rMal d 1 reduced symptoms significantly and enhanced IgG4/IgE ratios. Therapeutic benefits of SLIT for food allergy and pollen-food allergy syndrome include moderate efficacy, favorable safety, and variable tolerability; however, further study to evaluate long-term outcomes, improve adherence, and develop new approaches that promote more robust clinical and immunologic effects is an important next step before broad clinical implementation.

Comparison of OIT and SLIT: Efficacy, Safety, Tolerability

The available evidence directly comparing outcomes of OIT and SLIT is limited and includes one retrospective analysis of peanut OIT vs. SLIT, and randomized controlled trials comparing milk and peanut OIT vs. SLIT [28, 29, 98]. In the retrospective comparison of peanut OIT and peanut SLIT, investigators reported that after 2 years of therapy, OIT induced more robust immunologic changes than SLIT in peanut allergic children [98]. The more robust effects on peanut-specific IgE, IgG4, IgE/IgG4 ratios, and basophil reactivity were associated with more robust clinical effects. In a 2012 study comparing milk SLIT versus milk OIT in 30 pediatric subjects, Keet and colleagues observed that milk SLIT was associated with fewer side effects, but with the tradeoff of modest therapeutic efficacy [28]. Conversely, OIT was associated with increased therapeutic efficacy, but with higher risk of systemic side effects requiring therapeutic intervention. In the milk OIT treated group, 14/20 subject were able to pass an 8 g oral food challenge after therapy, compared with 1/10 in the milk SLIT group. Although the overall reported reaction rate was similar, individuals treated with SLIT reported primarily oropharyngeal, often self-limited symptoms, while OIT-treated subjects were more likely to report respiratory, gastrointestinal, or systemic reactions that

Table 1 Comparison of OIT and SLIT for the treatment of food allergy

	OIT	SLIT
Allergens	Milk, egg, peanut (others: wheat, tree nuts, fish, multi-allergen)	Peanut, milk, hazelnut, fruits
Maintenance dose	300–4000 mg	1–10 mg
Side effects	GI, oral (systemic, fever, exercise)	Oral-pharyngeal
Desensitization	Robust effect	Lesser effect
Sustained unresponsiveness	Impact in subset	Unknown
Immune modulation	Significant	Present

required treatment. When evaluating peanut SLIT and OIT in a randomized controlled trial, Narisety and colleagues observed similar findings to those observed when milk was the target allergen [29]. In this trial, 21 subjects underwent dose escalation to a target peanut dose of 3.7 mg for SLIT and 2000 mg for OIT. Only 16/21 subjects completed the 12-month double-blind portion of the trial. All completers had a >10-fold increase in threshold dose during OFC; however, the most robust increases in threshold dose were observed in the peanut OIT group compared with SLIT (141- vs. 22-fold). Adverse reactions were more frequent and more commonly required treatment in the OIT group, which also had increased risk of intolerable gastrointestinal side effects necessitating study withdrawal. Thus, the favorable safety profile associated with SLIT comes at the expense of reduced efficacy; conversely, the more robust desensitization observed with OIT comes at the risk of potentially intolerable, treatment-limiting side effects (Table 1). Optimizing future therapies will require developing approaches that couple the beneficial efficacy of OIT with the favorable safety profile of SLIT, potentially through the use of combination therapies, adjuvants, or alternative delivery methods.

Conclusion

Significant advances in development of active therapies such as OIT and SLIT for IgE-mediated food allergy have brought the field into an exciting era with licensed active therapies on the horizon, providing hope and optimism for food allergic patients and families. However, it should be noted that these approaches are not without associated risk and are presently considered experimental. Advances in our understanding of the immunologic mechanisms underlying food allergy and of the complexities of mucosal immune regulation will further inform the refinement of existing approaches and development of novel, next-generation therapeutic strategies.

Continued investigation is critical to address existing knowledge gaps including optimal dose, duration, maintenance regimen, long-term outcomes, predictors of response, cost-effectiveness, and psychosocial impact that will maximize efficacy, minimize risk, and develop individualized approaches for future clinical application.

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