



Oral and sublingual immunotherapy for food allergy

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Purpose of review

To critically appraise the recent most relevant studies in the rapidly advancing field of food oral and sublingual immunotherapy.

Recent findings

Food allergen-specific immunotherapy via oral (OIT) and sublingual route (SLIT) increases the threshold of reactivity to peanut, cow's milk, egg, wheat, and many other foods in the majority of the treated individuals. This desensitized state is contingent upon the continued ingestion of the maintenance doses of the food. Permanent oral tolerance is achievable in a smaller subset of the treated individuals. The optimal duration of therapy has not been firmly established but is likely dependent on the phenotype (severity and persistence). Efficacy of food-OIT is superior compared with SLIT, whereas the safety of OIT is less favorable. Standardization of treatment protocols, maintenance dosing, duration of therapy, target populations and harmonization of the outcomes are top priorities at this stage.

Summary

OIT and SLIT represent two different routes of food allergen-specific immunotherapy. Although significant progress has been made in the last decade, both treatment modalities are still in the very early stages of development and further investigations are necessary to optimize the protocols and improve safety while maximizing efficacy.

Keywords

food allergy, immunotherapy, milk, oral immunotherapy, peanut, sublingual immunotherapy

INTRODUCTION

The field of food allergen-specific immunotherapy exploded in the past 2 decades in response to the increasing recognition of the global burden of food allergy. Food allergy has become an important public health problem in the countries with the western life style and the prevalence is increasing worldwide, contributing to the so-called second wave of allergy epidemic [1]. In this article, we will review the selected recent advances in oral and sublingual immunotherapy for food allergy.

Oral immunotherapy

The first published report of the allergen-specific immunotherapy dates back to 1908, when Schofield described successful oral desensitization in a teenage boy with anaphylactic egg allergy [2]. The renewed interest in OIT emerged in the early 2000s and was followed by clinical trials of OIT to various foods, including peanut, cow's milk and egg white as well as OIT to multiple foods [3–5]. Additional foods included OIT to wheat, tree nuts, and sesame, among others [6,7⁸,8,9]. Details of the selected

important trials were reviewed elsewhere [10,11]. These clinical trials established the efficacy of OIT in inducing desensitization in the majority of the treated subjects following 1–2 years of treatment with daily doses of food allergen [12⁹]. Desensitization is defined as a temporary state of increased food allergen threshold contingent upon continued OIT [13]. Some of the studies assessed the more persistent treatment effect upon discontinuation of therapy for a period of several weeks (usually 2–8 weeks), referred to as 'sustained unresponsiveness', a surrogate term for permanent oral tolerance [14]. For milk

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Curr Opin Allergy Clin Immunol 2019, 19:000–000

DOI:10.1097/ACI.0000000000000587

KEY POINTS

- OIT and SLIT represent two different routes of food allergen-specific immunotherapy that differ in dosing schedule, daily maintenance dose, efficacy and safety profile.
- OIT is considered to have higher efficacy in inducing desensitization but carries a risk of anaphylaxis and eosinophilic esophagitis and requires significant life-style modifications.
- Combining OIT with biologics, such as omalizumab, dupulimab or probiotics may improve the risk/benefit ratio.
- The big advantage of SLIT is the safety profile, particularly low risk of anaphylaxis, paucity of gastrointestinal adverse events and no reports of eosinophilic esophagitis, suggesting that SLIT might be an option for the vulnerable patients.

and egg, these studies failed to demonstrate that OIT significantly shortened the duration of the disease in young children [15,16].

The large-scale, international clinical trials were initiated by the company manufacturing a standardized peanut powder for OIT (AR101). The pivotal phase III clinical trial of peanut OIT (PALISADE ClinicalTrials.gov number, NCT02635776) included 496 pediatric and 55 adult individuals with peanut allergy confirmed by dose-limiting symptoms to 100 mg or less of peanut protein during the baseline double-blind placebo-controlled food challenge (DBPCFC) [17^{***}]. The participants were randomized 3:1 to receive an active OIT with AR101 or placebo. The daily maintenance dose (DMD) was 300-mg peanut protein, an equivalent of approximately one peanut kernel. The trial met its primary endpoint of desensitization to 600-mg peanut protein. Significantly greater proportion, 250 of 372 pediatric participants on active OIT (67.2%), compared with five of 124 (4.0%) on placebo, were able to ingest a dose greater or equal to 600-mg peanut protein, without dose-limiting symptoms at the exit DBPCFC [difference, 63.2%; 95% confidence interval (CI): 53.0–73.3; $P < 0.001$]. In addition, symptom severity was lower at the exit food challenge than placebo. Efficacy was not shown in the participants 18 years of age or older. Adverse events during the intervention period were more common in the actively treated pediatric participants compared with placebo. In particular, severe adverse events were reported in 4.3% of active OIT and 0.8% of placebo. Overall, 43 participants (11.6%) in the active-drug group and three (2.4%) in the placebo group withdrew from the trial because of adverse

events during the intervention period. Sixteen participants in the active group (4.3%) withdrew from the trial due to chronic or recurrent gastrointestinal symptoms; three underwent esophagogastroduodenoscopy and eosinophilic esophagitis (EoE) was confirmed in one participant.

AR101 is currently under review by the Food and Drug Administration (FDA) in the United States. If AR101 receives FDA approval, it will become the first commercial biologic therapy for food allergy.

Safety of oral immunotherapy

OIT is associated with an increased risk of adverse events compared with placebo treatment or avoidance [11,18,19]. OIT adverse events range from anaphylaxis to delayed gastrointestinal symptoms of nausea, abdominal pain, vomiting, and diarrhea; in approximately 4% there is a formal diagnosis of EoE [11,20,21]. EoE may also occur during OIT with omalizumab pretreatment [22]. The gastrointestinal symptoms are the most common cause leading to the discontinuation of OIT and it appears that OIT may be unmasking or intensifying an underlying GI eosinophilic inflammation [22]. Prior to the initiation of OIT, among 21 asymptomatic peanut-allergic adults, esophageal eosinophilic inflammation [more than five eosinophils per high-power field (eos/hpf)] was detected in five (24%) [23]. Three (14%) participants had >15 eos/hpf associated with mild endoscopic findings (edema, linear furrowing, or rings) and some also demonstrated basal cell hyperplasia, dilated intercellular spaces, and lamina propria fibrosis. Increased eosinophils were found in the stomach (>12 eos/hpf) or duodenum (>26 eos/hpf) in nine subjects (43%). This study highlighted the vulnerability of food allergic patients to OIT inducing and/or unmasking GI eosinophilic inflammation. The recent meta-analysis of 12 peanut OIT trials [$n = 1041$; median age across trials 8.7 years (interquartile range 5.9–11.2)] showed with high certainty that OIT vs. no OIT, increased anaphylaxis risk [risk ratio 3.12 (95% CI: 1.76–5.55)], anaphylaxis frequency [incidence rate ratio 2.72 (1.57–4.72)], and epinephrine use [risk ratio 2.21 (1.27–3.83)] similarly during build-up and maintenance (P for interaction = 0.92). OIT also increased vomiting: risk ratio 1.79 (95% CI: 1.35–2.38) and angioedema: 2.25 (1.13–4.47), with high certainty [24^{***}]. Quality of life was not different between groups both for combined parents and participant self-report. The meta-analysis confirmed efficacy of peanut OIT in inducing desensitization; passing a supervised post-treatment challenge, was more likely with OIT; risk ratio 12.42 (95% CI: 6.82–22.61), high-certainty. The results of peanut OIT meta-analysis regarding

safety and adverse events profile are consistent with prior reports of OIT to cow's milk, egg, wheat and OIT to multiple foods from clinical trials as well as from clinical practice. It remains to be seen, whether frequency and severity of the adverse events decrease with longer duration of maintenance OIT and with more targeted selection of patients for OIT based on the novel biomarkers or food allergy phenotypes [25–27]. Recently, a policy decision by the Institute for Clinical and Economic Research issued to the public on 10 July 2019, demoted the grading of risk-benefit ratio of investigational peanut immunotherapy regimens to a 'D' (https://icer-review.org/announcements/peanut_evidence_report/), meaning a negative evaluation of the therapy. The report was criticized by a diverse group of investigators as premature and based on an incomplete review of the available evidence from trials as well the real-life experience [28].

A small, short-term (6 months) single center study of peanut OIT randomized the participants and caregivers 1:1 to receive information about non-life-threatening symptoms during OIT either as side effects or as potential indicators of desensitization; these families also participated in activities to reinforce these mindsets. Both groups received identical training regarding management of symptoms [29[¶]]. The group that was given the information that non-life-threatening symptoms during OIT could indicate desensitization was less anxious, less likely to contact staff about symptoms [5/24 (9.4%) vs. 27/154 (17.5%) events; $P=0.036$], experienced fewer non-life-threatening symptoms as doses increased ($B_{\text{Interaction}}=-0.54$, 95% CI: -0.83 to -0.27 ; $P<0.001$), less likely to skip/reduce doses [1/26 (4%) vs. 5/24 (21%) patients; $P=0.065$], and showed a greater increase in patient peanut-specific blood IgG4 levels ($B_{\text{Interaction}}=0.76$, 95% CI: $0.36-1.17$; $P<0.001$). Another study found that a structured written instruction plan can significantly reduce the risk of adverse reactions during the maintenance phase of oral immunotherapy, still maintaining the beneficial effect of treatment [30]. These results suggest that communication styles regarding the expected non-life-threatening side effects during desensitization may influence the participants' and their caregivers' perceptions and improve their experience during OIT.

Optimal dose and age at initiation of oral immunotherapy

Limited evidence suggests that low dose (300-mg peanut protein) peanut OIT in preschool children is as efficacious and better tolerated than high dose (3000-mg peanut protein) [31]. Long-term dosing in

older subjects treated with multi food OIT with DMD 300-mg food protein were as likely as those on high DMD (median 2-g food protein) to ingest 2-g protein of each food allergen protein during oral food challenges (OFC) performed at the end of the follow-up period of 36–72 months [32]. In a study evaluating the feasibility, efficacy and safety of high-dose peanut OIT, only 21.1% of 77 children (5–15 years) reached the DMD of 5000-mg peanut protein [33[¶]]. Distaste for peanuts and adverse events, including high risk of anaphylaxis, limited the feasibility of reaching high dose DMD.

Quality of life as an outcome of food oral immunotherapy

Health-related quality of life (HRQL) has emerged as the potential outcome of interest in food OIT trials [34]. The evidence to date has been rather inconclusive, although some studies reported improvement in HRQL of the caregivers, measured by the food allergy quality of life questionnaire-parental form (FAQLQ-PF) but not the peanut-allergic patients [35]. In an Israeli study of 191 children 4–12 years undergoing OIT, FAQLQ-PF improved significantly upon reaching maintenance compared with baseline, while no change was observed among control, untreated children. Worse baseline FAQLQ-PF score, single food allergy and a younger age were associated with greater improvement. Considering the heterogeneity of the factors that influence HRQL, a uniform approach incorporating precisely defined HRQL and other patient-related outcomes is needed to compare efficacy of food allergy treatments between different studies.

Oral immunotherapy with omalizumab and probiotics

There is a growing interest in combining food-specific OIT with biologic therapies [36,37]. This strategy is aimed at enhancing efficacy and improving safety of treatment. To date, the published data support the combination of OIT and anti-IgE mAb [38–40]. In a phase two single-center trial, participants, aged 4–15 years, with multifood allergies documented by a positive DBPCFC at 500 mg or less of food protein, were randomized (3 : 1) with a block size of four, to receive multifood OIT to two to five foods, together with omalizumab ($n=36$) or placebo ($n=12$) [41[¶]]. Omalizumab or placebo was administered subcutaneously for 16 weeks, with OIT starting at week 8, and was stopped 20 weeks before the exit DBPCFC at week 36. The primary endpoint was the proportion of participants who passed DBPCFC to at least two of their offending foods. At week 36, a

significantly greater proportion of the omalizumab-treated [30 (83%) of 36] vs. placebo [four (33%) of 12] participants passed DBPCFC to 2-g protein for two or more of their offending foods (odds ratio 10.0, 95% CI: 1.8–58.3, $P=0.0044$). All participants completed the study. There were no serious or severe (grade three or worse) adverse events and no withdrawals. Participants in the omalizumab group had a significantly lower median per-participant percentage of oral immunotherapy doses associated with any adverse events (27 vs. 68%; $P=0.0082$). The most common adverse events in both groups were GI symptoms. This study suggested that omalizumab enables safe and rapid desensitization in allergic patients with multiple food allergies.

Significantly, in a real-life study of 15 children allergic to 37 foods were treated with omalizumab for severe asthma [42[¶]]. Omalizumab therapy was associated with increased threshold for milk, egg, wheat, and hazelnut from a mean (SD) 1012.6 ± 1464.5 mg protein to 8727 ± 6463.3 eliciting dose ($P < 0.001$). A total of 70.4% of subjects tolerated the OFC with a regular serving of the food after 4 months of treatment with omalizumab. These foods were reintroduced in the patients' diet without the need for any OIT procedures. The remaining foods were partially tolerated. This uncontrolled study supports the potential of anti-IgE as a monotherapy for a subset of patients with food allergy [43].

Peanut OIT in combination with probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 was evaluated in a phase two proof of concept randomized trial [44]. Intention-to-treat analysis showed that peanut OIT with probiotic led to sustained unresponsiveness (at 4 weeks) in 74% of treated subjects and 84% of PPOIT-treated subjects achieved desensitization to a cumulative dose of 4-g peanut protein [44]. However, the study design was criticized for not including a proper control for probiotic, as the control group was treated with both placebo peanut OIT and placebo probiotic. A long-term follow-up study enrolled 48 (86%) of 56 eligible participants [45]. Mean time since stopping treatment was 4.2 years in both groups. Participants from the peanut OIT with probiotic group were significantly more likely than those from the placebo group to have continued eating peanut [16 (67%) of 24 vs. one (4%) of 24; absolute difference 63% (95% CI: 42–83), $P=0.001$; number needed to treat 1.6 (95% CI: 1.2–2.4)]. Seven (58%) of 12 participants from the peanut OIT with probiotic group achieved 8-week sustained unresponsiveness, compared with one (7%) of 15 participants from the placebo group [absolute difference 52% (95% CI: 21–82), $P=0.012$; number needed to treat 1.9 (95% CI: 1.2–4.8)]. Considering substantially lower cost of

probiotic compared with omalizumab and other biologic therapies, OIT with probiotic may be an option for a subset of patients.

Guidelines for food oral immunotherapy

Despite the lacking pharmaceutical product for OIT and no standardized protocol of treatment, allergists in many countries provide OIT with commercially available food forms [46,47[¶],48–52,53[¶]]. This practice is driven by an unmet need and in response to high demand, mostly from the caregivers of children with food allergies [54[¶]]. The utilization of nonstandardized products is associated with potential significant variability in protein content [55]. A survey among the United States allergists indicated that the availability of a standardized product for OIT is important to the majority of them [56[¶]]. Several professional societies issued guidelines for food OIT, emphasizing the necessity of conducting food OIT in the practices with extensive expertise in food allergy and anaphylaxis [57,58^{¶¶},59–62].

Toward standardization of oral immunotherapy protocols and outcomes

Direct comparisons of primary outcomes, efficacy and safety parameters are confounded by the heterogeneity of the study design regarding the age of the participants, up-dosing schedule, DMD, duration of therapy, and reporting of treatment-emergent adverse events [63[¶]] (Fig. 1). Many of the investigator-initiated clinical trials were limited to the single-center and included relatively small number of participants. Long-term follow-up of the participants in clinical trials as well those treated on a clinical basis is need to better define the risk and benefit ratio of food OIT [12[¶],32,45,64]. There is an urgent need to harmonize the research efforts and to standardize the efficacy outcomes and reporting of the adverse events [65,66].

Sublingual immunotherapy with food extracts

SLIT is an accepted form of aeroallergen immunotherapy and has favorable safety profile compared with subcutaneous IT. Food SLIT involves holding a food protein solution sublingually for 2 min followed by swallowing it. Food SLIT includes a build-up and a maintenance phase, similar to food OIT.

The first single-center, double-blind, placebo-controlled SLIT trial for peanut allergy was published by Kim *et al.* [67] and the first study comparing cow's milk SLIT with OIT at two doses was published by Keet *et al.* [68]. Subsequently, multicenter studies of

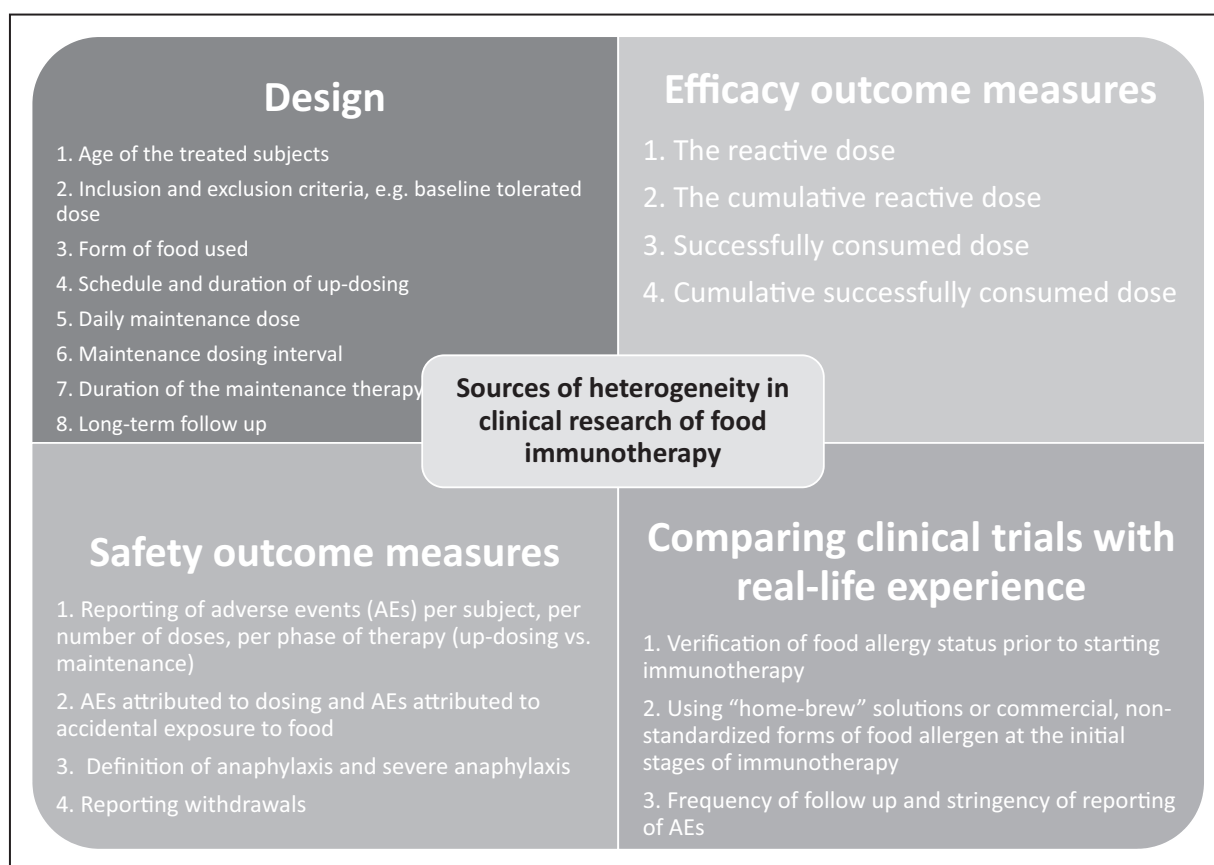


FIGURE 1. Selected issues affecting the ability to compare the results from different studies to illustrate the urgent need for harmonization of the clinical research in food immunotherapy.

peanut SLIT demonstrated that peanut SLIT was safe and that it was effective in a subset of the treated subjects [69,70]. Recently, Kim *et al.* [71^{***}] reported on a long-term (up to 5 years) peanut SLIT protocol with DMD 2-mg peanut protein. This study included 48 participants (median age 6.5 years) with history of clinical reaction to peanut and peanut-specific IgE of at least 7 kU/l at study entry. Eleven (22.9%) subjects withdrew from the study prior to exit DBPCFC, due to adherence issues ($n=8$), recurrent abdominal pain ($n=2$), and other reasons ($n=1$). Adherence in the 37 participants completing long-term SLIT was estimated at 95.5%. In the intention-to-treat analyses, 32 participants (66.7%) participants successfully consumed dose of at least 750 mg during exit DBPCFC, whereas 12 (25%) tolerated the 5000-mg OFC with 10 (20.8%) demonstrating sustained unresponsiveness at 4 weeks. Peanut SPT wheal, peanut-specific-IgE, and basophil activation to peanut decreased significantly compared with baseline values. Peanut SLIT was safe, with 4.8% of doses having associated symptoms (transient oropharyngeal pruritus); only 0.21% doses were treated with oral antihistamines, no epinephrine was administered and no EoE was reported. This study suggests that extended peanut SLIT

therapy is safe and provides clinically meaningful desensitization in the majority of peanut-allergic children and can provide SU in a subset of them.

Balancing act: direct comparison between oral immunotherapy and sublingual route

Side-by-side comparison of treatment protocols, DMD, efficacy and safety of OIT and SLIT is presented in Table 1. It is obvious that these two treatment modalities differ significantly and that each may appeal to a different target population, based on the individual preference and the risk/benefit ratio. The big advantage of SLIT is the safety profile, particularly low risk of anaphylaxis, paucity of GI adverse events and no reports of EoE, suggesting that SLIT might be an option for the vulnerable patients. In the future, adjuvants might increase SLIT efficacy that is currently limited by the volume of food extract that can be held under the tongue.

CONCLUSION

OIT and SLIT represent two different routes of food allergen-specific immunotherapy. While significant progress has been made in the last decade, both

Table 1. Side-by-side comparison of food allergen immunotherapy via oral and sublingual route

Treatment/parameters	OIT	SLIT
Maintenance dose	300–5000 mg	2–7 mg
Dosing interval	Daily	Daily
Up-dosing	Usually over 6 months	None or limited
Efficacy	Higher	Lower
Safety	Risk of systemic reactions (including anaphylaxis), gastrointestinal symptoms, EoE	Usually mild, local oropharyngeal pruritus, no reports of EoE

EoE, eosinophilic esophagitis; OIT, oral immunotherapy; SLIT, sublingual route.

treatment modalities are still in the very early stages of development and further investigations are necessary to optimize the protocols and improve safety while maximizing efficacy. The future is bright and effective therapy for food allergy patients is within reach.

Acknowledgements

None.

Financial support and sponsorship

None.

Conflicts of interest

There are no conflicts of interest.

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- of special interest
- of outstanding interest

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The long-term (up to 5 years) peanut sublingual route (SLIT) in children (median age 6.5 years)-induced desensitization to more than 750 mg peanut protein (equivalent to more than three peanut kernels) in 66.7%, desensitization to 5000 mg peanut protein (equivalent to a full serving of peanut butter) in 25%, and sustained unresponsiveness at 4 weeks in 20.8%, intention-to-treat-analysis. This study suggests that extended peanut SLIT therapy is safe and provides clinically meaningful desensitization in the majority of peanut-allergic children and can provide SU in a subset of them.