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Comparison of sublingual immunotherapy and oral immunotherapy in peanut allergy

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Abstract

The prevalence of food allergy has been increasing over the past few decades at an alarming rate with peanut allergy affecting about 2 % of children. Both oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) have shown promise as a treatment option for peanut allergy. Immunotherapy induces desensitization and reduces the risk of reaction during accidental ingestion and may also enable those who are successfully desensitized to include the food allergen in their diet. OIT has been very well studied and has been found to be more efficacious than SLIT with an acceptable safety profile. However, SLIT is associated with fewer side effects. Studies indicate that a combination of SLIT and OIT may together induce a significant increase in challenge thresholds with fewer adverse events. More head-to-head clinical trials that directly compare OIT and SLIT as well as SLIT and OIT combination studies are warranted.

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Introduction

The increasing trend in food allergy (FA) prevalence over the past few decades is a cause for concern and a public health problem [1]. It is a potentially life-threatening disease increasing anxiety and decreasing quality of life for participants and their caregivers [2]. FA is now estimated to affect between 4–11 % of infants and young children, with peanut allergy affecting about 2 % of children [3, 4]. Although the majority of children outgrow milk (68 %) [5] and egg (79 %) [6] allergies, the likelihood of outgrowing peanut allergy is much lower (27 %)[7]. The current standard of care for the management of FA involves strict elimination of the offending allergen and treating reactions due to accidental exposures with antihistamines and epinephrine. Allergen avoidance is difficult to accomplish because many allergenic foods, such as milk, eggs, and peanuts, are common ingredients in many foods. Accidental ingestion is common and a 10-year follow-up study found that 75 % of individuals with peanut allergy accidentally consumed peanuts, stressing the need for effective treatments [8]. Although not currently FDA-approved for FA, allergen-specific immunotherapy (AIT) has shown promise for treating FA [9].

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Abbrevations

AIT	Allergen-specific immunotherapy
BHR	Bronchial hyper-responsiveness
Bregs	B regulatory cells
DBPCFC	Double-blind placebo-controlled food challenge
FA	Food allergy
OIT	Oral immunotherapy
PPOIT	Probiotic with peanut OIT
SLIT	Sublingual immunotherapy
SU	Sustained unresponsiveness
Th	T-helper
Tregs	Regulatory T cells

In AIT, incremental doses of allergen are administered via various routes, such as oral, subcutaneous, sublingual, and epicutaneous [9]. Oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) have been the most common and best researched FA immunotherapies. Subcutaneous immunotherapy has been shown to be efficacious but it is no longer being actively investigated as a treatment for FA because of high adverse reactions [10]. Epicutaneous immunotherapy is a novel mode of FA treatment and preliminary results are promising [11]. The goal of early food immunotherapy trials was to achieve desensitization by increasing antigen threshold to levels that can prevent allergic reactions on accidental ingestion. The ultimate goal of immunotherapy for FA is to enable ingestion of food allergens in amounts that are commonly ingested in diets and to establish a state of permanent desensitization even after periods of discontinuation of allergen ingestion (tolerance). Currently, one of the limitations of immunotherapy for FA is that, in a number of individuals, continued ingestion of allergen appears necessary for maintenance of desensitization. As data on long-term follow up studies of OIT or SLIT is limited and biomarkers for establishing permanent tolerance are not currently available, current studies aim to establish sustained unresponsiveness (SU), defined as a sustained desensitization after a specified period of allergen avoidance [12, 13, 14]. A second limitation of AIT is the long treatment period (months to years), which is further magnified for the 30% of food-allergic individuals who have multiple allergies [3]. These limitations are being addressed by the use of novel adjuvants such as probiotics and anti-IgE antibodies.

Although the exact mechanisms underlying AIT is unclear, studies have indicated that they likely include skewing of T helper (Th) cell responses from a Th2 towards a Th1 cytokine profile, suppression of mast cell and basophil degranulation, upregulation of IL-10-producing regulatory T cells (Tregs) and B regulatory cells (Bregs), decreases in peanut-specific IgE, increases in peanut-specific IgA and IgG4, deletion of antigen-specific T cells, and suppression of late-phase effector cells such as eosinophils. Further details on mechanisms underlying allergic reactions to foods and desensitization with AIT can be obtained from a number of excellent reviews [15, 16, 17, 18, 19]. While OIT introduces allergens to the gastrointestinal tract and activates gut mucosal dendritic cells, SLIT mostly interacts through pro-tolerogenic Langerhans cells in the oral mucosa, and both modalities downregulate allergic responses through immunomodulation of tissue and circulating effector cells [18, 20]. In this review, we compare SLIT and OIT, the most common forms of immunotherapy, for peanut allergy. **Tab. 1** summarizes clinical trials of SLIT and OIT trials.

Oral immunotherapy

OIT is a promising treatment option for inducing desensitization in FA and for improving FA-related quality of life. Early studies evaluated safety of OIT with updosing to a maintenance dose of 800 mg of peanut protein (1 peanut contains about 240 [21] to 300 mg of peanut protein) [22]. The goal of these studies was to desensitize individuals and reduce risk of reaction on accidental ingestion. Subsequent studies increased maintenance doses up to 4,000 mg of peanut protein to desensitize individuals to amounts normally ingested in diets. In a peanut-OIT study published in 2009, Hofmann et al. [22] evaluated safety of peanut OIT in peanut-allergic children and found that significant allergic reactions were more likely during the initial escalation day than during the build-up or home dosing phase. Allergic reactions during home dosing were rare with only a 3.5 % risk of reaction (0.7 % of home doses needed treatment). On initial escalation day, 93 % (26/28) experienced symptoms with upper respiratory (79 %) and abdominal (68 %) being the most common symptoms. 71 % completed the study. In a subsequent study of peanut OIT by Jones et al., participants similarly updosed to a maintenance dose of 300 mg peanut protein and continued on this dose until food challenge. The daily maintenance dose was subsequently increased to 1,800 mg in those participants whose peanut IgE remained >2 kU/L after 12 months on maintenance dose. 29 out of the 39 participants completed the protocol and 27 passed OFC of 3,900 mg peanut protein. [21].

The first randomized, double-blind, placebo-controlled study to investigate the safety and effectiveness of peanut OIT in children was reported in 2011 by Varshney et al. After the initial escalation day, participants in the active group were updosed to a much higher maintenance dose (4,000 mg peanut protein) than that of previous studies. Sixteen of the 19 OIT-treated participants completed the 1 year protocol and passed the 5,000 mg OFC, while the 9 placebo-treated participants ingested a much lower dose (median cumulative dose of 280 mg) indicating effectiveness of peanut OIT in inducing desensitization to doses normally ingested in diets. None of the OIT participants required epinephrine or hospitalization [23]. A phase 2 randomized controlled trial (STOP II) of peanut OIT was conducted by Anagnostou et al. in 2014. At the end of 24 weeks, 39 of 49 participants in the active group reached the maintenance dose of 800 mg and 24 successfully completed post-OIT (DBPCFC, double-blind placebo-controlled food challenge); however, 0 of 50 controls achieved desensitization. Par-

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Tab 1: Summary of major OIT and SLIT Trials in Peanut Allergy

Author (year)	Design	n Age (years)	Outcome
			Oral immunotherapy
Hofmann et al. [22] (2009)	Open label	n (active) = 28 Age = 1.1–9.4 (mean 4.8)	Updosing: 28/28 completed the initial day rush protocol (0.1 mg to a maximum of 50 mg peanut protein) and 25/28 completed the buildup and home updosing phase to 300 mg Maintenance phase: 20/28 completed maintenance phase (4 or 12 months)
Jones et al. [21] (2009)	Open label	n (active) = 39 Age = 1–9.25 (median 4.8)	Updosing: 10/39 completed initial day escalation day (0.1 to 50 mg) and 29/39 completed the buildup phase to 300 mg peanut protein maintenance. Maintenance dose was 300 mg for 12 months, then 1,800 mg if peanut IgE remained >2 kU/L after 12 months on maintenance dose. Maintenance phase: 29/39 were on maintenance phase for 4–22 months (median 4.7 months) and underwent food challenge Post OIT: 27/39 passed food challenge to 3900 mg peanut protein at end of maintenance phase
Blümchen et al. [42] (2010)	Open-label	n (active) = 23 Age = 3.2–14.3 (median 5.6)	Updosing: 5/23 completed rush protocol (up to 7 days) and 14/23 completed long-term buildup protocol (up to 20 months) and achieved a maintenance dose of at least 500 mg whole peanut in 0–560 days (median 7 months) Maintenance dose: 14/23 completed 8 weeks of a maintenance dose (range 7–13 weeks) and then a 2-week (range 14–22 days) allergen avoidance period before undergoing final DBPCFC. Post-OIT: Median final DBPCFC threshold values in all 14 participants were significantly increased from baseline DBPCF (1,000 mg vs 190 mg whole peanuts, respectively)
Varshney et al. [23] (2011)	Randomized, double-blind, placebo-controlled, multicenter trial	n (active) = 19 n (placebo) = 9 Age (active) = 3.2–10.5 (median 7.0), Age (placebo) = 2.3–9.5 (median 5.8)	Updosing: 16/19 of active group reached the 4,000 mg maintenance dose. Maintenance: 16/19 of active group completed 4,000 mg maintenance dose for 1 month and underwent food challenge (11.3 to 16.3 months, median 12.4 months) after start of trial. Post-OIT: 16/19 of active group passed OFC to 5,000 mg peanut protein. The median cumulative dose ingested by the placebo group was 280 mg
Anagnostou et al. [43] (2011)	Open label	n (active) = 22 Age = 4–18	Updosing: 21/22 completed gradual updosing (range: 56–264 days, median 140 days) to maintenance dose of 800 mg peanut protein. Maintenance: 19/22 and 18/22 completed 6 and 30 weeks, respectively, at 800 mg of peanut protein maintenance dose and underwent food challenge. Post-OIT: 12/22 and 14/22 passed OFC after 6 (2,600 mg) and 30 (6,600 mg) weeks, respectively, on a maintenance dose
Schneider et al. [33] (2013)	Open-label phase 1. Omalizumab treatment 12 weeks before and 8 weeks after initiation of OIT. Omalizumab stopped at week 20	n (active) = 13 Age = 8–16 (median 10)	Updosing:13/13 reached 500 mg peanut flour (peanut flour is approximately 50 % peanut protein) dose during day 1 rush desensitization and 12/13 reached 4,000 mg peanut flour maintenance dose at week 20 Maintenance: 12/12 continued 4,000 mg peanut flour maintenance dose for an additional 12 weeks and underwent food challenge. Post-OIT: 12/13 passed OFC to 8000 mg peanut flour
Vickery et al. [26] (2014)	Open label follow-up study of Jones et al. [21] (2009)	n (active) = 39 Age = 1–9.25 (median 4.8)	Follow-up: 24 of the 27 participants who passed 3,900 mg peanut protein food challenge at end of maintenance phase continued on a maintenance dose (protocol was modified to allow for 4,000 mg) for a total of up to 5 years of OIT. After 1 month of discontinuation of OIT, 12/24 passed 5,000 mg food challenge indicating SU
Anagnostou et al. [24] (2014)	Phase 2, randomized placebo-controlled, cross-over trial	n (active) = 49 n (placebo) = 50 Age = 7–16	Updosing and maintenance: Phase I: 39/49 of active group reached a maintenance dose of 800 mg, completed a total of 26 weeks OIT and underwent food challenge Phase II (open cross over): 91 % reached maintenance dose of 800 mg protein. Post-OIT: Phase I: 24/39 of the active group and 0/50 of the control group passed 1,400 mg food challenge with peanut protein Phase II (open cross-over): 54 % tolerated 1400 mg peanut challenge with peanut protein
Tang et al. [30] (2015)	Randomized, placebo-controlled (Adjuvant: *Lactobacillus rhamnosus*)	n (active) = 31 n (placebo) = 31 Age (active) = mean 6.1 (SD 2.4) Age (placebo) = mean 5.8 (SD 2.6)	Updosing: In the active group, 30/31 completed rush updosing with buildup phase to 2 g peanut protein in 8.3–11.8 (median 8.9) months. Maintenance phase: 29 of active group completed maintenance phase in 18.2–19.9 months (median 18.8) and underwent food challenge Post-OIT: 26/31 passed food challenge to 4 g cumulative peanut protein at end of maintenance phase. 23/31 passed a second food challenge to 4 g cumulative peanut protein after 2–5.3 (median 2.3) weeks of a peanut elimination diet to achieve SU. In the placebo group only 1/31 achieved SU

Author (year)	Design	n Age (years)	Outcome
MacGinnitie et al. [34] (2016)	Randomized-placebo-controlled. Participants treated with omalizumab 12 weeks before and 8 weeks after initiation of OIT	n (omalizumab group): 29 n (placebo group): 8 Age (omalizumab group): 7–19 (median 10) Age (placebo group): 6–17 (median 10)	Updosing: 23/29 of omalizumab group completed rush desensitization to 250 mg and reached 2,000 mg peanut protein maintenance dose (week 12-through week 26). Omalizumab was stopped after reaching maintenance dose. Maintenance: 23/29 of omalizumab group continued 2,000 mg maintenance dose for an additional 6 weeks after omalizumab discontinuation and underwent food challenge. Post-OIT: 22/29 (active) and 1/8 (placebo), respectively, passed food challenge to 4,000 mg 12 weeks after omalizumab discontinuation
Vickery et al. [27] (2017)	Randomized, double-blind	n = 37 (300 mg low dose = 20, 3000 mg high dose 17) Age = 0.75–3 (median 2.4)	Updosing: 36/37 completed updosing to a maintenance dose of either 300 mg or 3,000 mg peanut protein. Maintenance: 32/37 completed maintenance dose and underwent food challenge Post-OIT: 30/37 (low dose 17/20 and high dose 13/17) passed OFC (5,000 mg); Overall 29/37 (low dose 17/20 and high dose 12/17) achieved SU after 4 weeks of peanut avoidance after a median of 29 months of treatment
Kukkonen et al. [25] (2017)	Controlled	n (active) = 39 n (placebo) = 21 Age = 6–18	Updosing: 33/39 completed gradual updosing from 0.1 mg to maintenance dose of 4 peanuts. Median updosing time was 269 days (range 223–486 days) Maintenance: 31/39 completed 4 weeks on maintenance dose of 4 peanuts and completed the DBPCFC Post treatment: 26/39 passed DBPCFC to 5,000 mg peanut (1,255 mg protein); 0/21 controls were desensitized
Bird et al. [29] (2017)	Randomized double-blind placebo-controlled study of a formulated and well-characterized formulation of peanut protein (AR101)	n (active) = 29 n (placebo) = 26 Age = 4–26	Post-OIT: 23/29 and 18/29 of tolerated ≥ 443 mg and 1,043 mg at exit DBPCFC, respectively (after reaching a maintenance dose of 300 mg over 20–34 weeks and tolerating it for an additional 2 weeks). In the placebo-treated group, 5/26 and 0/26 tolerated ≥443 mg and 1,043 mg at exit DBPCFC, respectively
Nagakura et al. [28] (2017)	Open-label, historical control group	n (active) = 22 n (placebo) = 11 Age (active) = median 8.5 Age (control) = median 7.9	Updosing: 5/22 and 22/22 reached a maintenance dose of 795 mg after rush updosing (5–12 days) and long-term buildup phase (up to 12 months), respectively. Maintenance: 22/22 reached desensitization (defined as the ability to consume 795 mg of peanut protein after discontinuation of premedication) by 8 months on maintenance phase (median 3 months) Post-OIT: After 2 weeks of peanut avoidance, 15/22 of the active group passed OFC (795 mg of peanut protein or 3 g whole peanut). In the control group, only 2/11 passed OFC
Hsaio et al. [31] (2017)	Follow-up study of Tang et al. [30]	n (active) = 24 n (placebo) = 24	Follow-up: In a 4-year follow-up study, participants from the PPOIT group were significantly more likely than those from the placebo group to have continued eating peanut (16 out of 24 vs 1 out of 24, respectively) and attain 8 week SU (7 of 12 vs 1 of 15 from the placebo group, respectively)
Sublingual immunotherapy			
Kim et al. [37] (2011)	Randomized, double-blind, placebo-controlled	n (active) = 11; n (placebo) = 7 Age (active) = median 5.8 (range 2.8–10.5); Age (placebo) = median 4.7 (range 1.6–7.4)	Updosing: 11/11 of active participants completed updosing to a maximum maintenance dose of 2.0 mg of peanut protein. Maintenance: 18/18 participants completed 12 months of dosing and underwent 2,500 mg peanut challenge Post-OIT: Median cumulative ingested dose for active group was 1,710 mg of peanut protein. For the placebo group, it was 85 mg
Fleischer et al. [38] (2013)	Randomized, double-blind, placebo-controlled multicenter trial	Phase I n (active) = 20 n (placebo) = 20 Phase II n (active) = 20 n (placebo cross-over) = 16 Age = 15.0 (range 12.2–36.8)	Phase I (0–44 weeks) Peanut-SLIT group (maximum maintenance dose 1,386 mg peanut protein): 14/20 participants receiving peanut SLIT were respondersa and their median successfully consumed dose increased significantly from 3.5 to 496 mg. Placebo group: 3/20 receiving placebo were responders and their median successfully consumed dose increased from 71 to 146 mg (non-significant). Phase II (44–68 weeks): Peanut-SLIT continuation group (maximum maintenance dose 1,386 mg peanut protein): Median successfully consumed dose significantly increased to 996 mg. Cross-over placebo group (maximum maintenance dose 3,696 mg peanut protein; 44–68 weeks): 7/16 crossover subjects were responders; Median successfully consumed dose increased from 21 to 496 mg among responders
Burks et al. [39] (2015)	Follow up study to Fleischer et al. [38]	n (active) = 20 n (high dose crossover arm) = 17 Age = 15.0 (range 12.2–36.8)	Follow-up: Oral food challenge was performed at 3 year follow-up. After 3 years, SLIT was discontinued for 8 weeks after which another food challenge was performed. 4/37 achieved SU. Rate of withdrawal from the study was high (>50 %)

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Author (year)	Design	n / Age (years)	Outcome
Sublingual and Oral immunotherapy			
Chin et al. [44] (2013)	Retrospective comparative study of published studies (Varshney et al. [23] and Kim et al. [37]). This new analysis included additional participants from those included in the earlier study	Participants undergoing 12-month DBPCFC n (OIT) = 18 n (SLIT) = 27	12-month DBPCFC: OIT-treated participants were 3 times more likely to pass the 12-month desensitization DBPCFC than SLIT-treated participants. In addition, eliciting dose thresholds were lower and more variable during DBPCFC in SLIT-treated participants, compared to OIT-treated participants
Narisety et al. [40] (2015)	Randomized Placebo-controlled, double-blind (active SLIT/placebo OIT or active OIT/ placebo SLIT)	n (active OIT/placebo-SLIT) = 11 n (active SLIT/placebo OIT) = 10 Age = 7–13	Updosing: 10/11 active OIT completed 16 weeks updosing to a maintenance goal of 2,000 mg peanut protein, 10/10 of active SLIT completed 16 weeks updosing to a maintenance dose of 3.7 mg. Maintenance dose: 7/11 of the active OIT group and 9/10 of the active SLIT group completed 12 months of maintenance dosing and underwent food challenge Post-OIT: 7/11 of the active OIT group and 9/10 of the active SLIT group achieved the primary endpoint of a 10-fold increase in baseline after 12 months of maintenance dose. The median challenge dose in the active OIT group was significantly higher than the active SLIT group (141-fold vs 22-fold, respectively). SU (4 weeks of an elimination diet): SU was determined in eligible participants after 12 months or 18 months (in those with extended maintenance periods). In the final analysis 3/11 of active OIT and 1/10 of active SLIT achieved SU

**Responders were defined as participants with a 10-fold increase in successfully consumed dose or those successfully consuming 5,000 mg peanut powder (about 2,500 mg peanut protein).*

ticipants in the control group who were allergic to peanuts were subsequently offered peanut OIT during a second open-label cross-over phase of the study. At the end of the second phase, 54 % of the participants passed a 1,400 mg food challenge to peanut protein and 91 % tolerated an 800 mg daily dose [24]. A 2017 placebo-controlled study evaluated bronchial hyper-responsiveness (BHR) and airway inflammation as an aspect of peanut OIT safety. In this study, 33 of the 39 OIT-treated participants reached a daily maintenance dose of 4 peanuts and 67 % passed the post treatment OFC of 5,000 mg peanut powder (1255 mg protein) at the 8 month DBPCFC, while none of the 21 controls were desensitized. There was no change in lung function and BHR tended to be alleviated, but the change was not statistically significant. These results indicated that peanut OIT was effective for severe allergy with no harmful effect on BHR or airway inflammation [25].

To assess whether the protective effect of peanut OIT is sustained after stopping treatment, a follow-up study of participants who were successfully desensitized [21] was conducted by Vickery et al. As mentioned earlier, in the study by Jones et al. [21], 29 out of the 39 participants completed the protocol and 27 passed OFC of 3,900 mg peanut protein. These participants were then maintained at a dose of 4,000 mg peanut protein for up to 5 years and then asked to discontinue the maintenance dose for 1 month. In all, 24 participants successfully completed the protocol, and 12 participants passed the food challenge 1 month after OIT discontinuation. This was the first study to demonstrate sustained unresponsiveness (SU) after peanut OIT [26]. In a second study, Vickery further evaluated SU as well as the safety, effectiveness, and feasibility of early peanut OIT in preschool children. Forty peanut-allergic preschool children aged 9–36 months were enrolled in a double-blind, randomized OIT trial and block-randomized 1 : 1 to receive treatment at goal daily maintenance doses of 300 or 3,000 mg peanut protein. SU was assessed 1 month after stopping treatment. Success was reported in suppressing allergic immune responses with both tested doses. Seventeen of 20 children in the low-dose group and 13 of 17 in the high-dose group were desensitized, while 17 of 20 and 12 of 17, respectively, achieved SU [27], indicating that 300 mg/day was as effective as 3,000 mg/day. This has clinical implications as a lower maintenance dose is likely to lead to better long-term compliance. A study by Nagakura et al. [28] evaluated SU in participants with confirmed anaphylactic symptoms. The historical control group consisted of 11 participants with anaphylaxis by OFC who underwent a second OFC after 2 years. Twenty-two Japanese children with peanut allergy, aged 6–18 years, all of whom demonstrated anaphylaxis during a baseline DBPCFC, were enrolled to receive peanut OIT. After the initial rush phase (5–12 days) in hospital, patient administered peanut at home during the long-term build-up phase (0–12 months). Daily ingestion dose

was gradually increased to a maintenance dose of 795 mg of peanut protein. By 8 months, all participants were desensitized, which was defined as being able to consume 795 mg peanut protein without symptoms after stopping premedication. All participants completed the protocol. Fifteen out of 22 participants passed the second OFC after 2 weeks of peanut elimination and achieved SU. In the control group, only 2 of 11 participants passed OFC.

Peanut OIT protocols and peanut allergen doses have as yet not been standardized among studies, which have variably used whole peanuts, peanut flour, protein, or powder. AR101 is a peanut product developed by Aimmune. It consists of defatted lightly roasted peanut flour with the relative antigen potency of Ara h1, Ara h2, and Ara h6 kept uniform. In 2017, Bird et al. [29] published the first randomized, double-blind, placebo-controlled phase 2 clinical trial to assess the safety and efficacy of AR101 in peanut OIT. Fifty-five participants aged 4 to 26 years were enrolled at 8 US centers, with 29 participants receiving AR101 and 26 receiving placebo. Eighteen of 29 AR101-treated and 0 of 26 placebo-treated participants tolerated 1,043 mg peanut protein, respectively, at exit DBPCFC. Compared with placebo, AR101 significantly reduced symptom severity during exit DBPCFCs.

Oral immunotherapy with adjuvants

As mentioned earlier, some of the limitations of OIT are the recurrence of peanut sensitization after a period of peanut avoidance or elimination and the lengthy treatment period. To address these limitations, adjuvants such as probiotics and other biologics have been evaluated in clinical trials. Tang et al. co-administrated a probiotic (*Lactobacillus rhamnosus* CGMCC 1.3724) with peanut OIT (PPOIT) in a randomized, double-blind, placebo-controlled trial. Sixty-two peanut-allergic children aged 1–10 years were randomized 1 : 1 into a treatment or placebo group and underwent PPOIT for 18 months. The active group received a fixed daily dose of probiotic together with OIT, while the placebo group received placebo only. DBPCFC of 4,000 mg peanut protein was performed at the last day of treatment and at 2 or more weeks after stopping treatment. SU was achieved in 23 of 28 treated participants and 1 of 28 placebo-treated participant [30]. The study concluded PPOIT was effective at inducing SU compared with placebo [30]. A 4-year long-term follow-up study of treatment cessation of eligible participants from the PPOIT study was recently published. The study found that participants from the PPOIT group were significantly more likely than those from the placebo group to have continued eating peanut (16 out of 24 vs 1 out of 24, respectively) and attain 8 week SU (7 of 12 vs 1 of 15 from the placebo group, respectively) but less likely to have allergic reactions (4 out of 24 vs 6 out of 24, respectively). None of the participants had anaphylactic reactions. These results indicate that PPOIT provides long-term SU after cessation of treatment. A drawback of the study was a lack of a probiotic group (without OIT) to clarify the relative contributions of probiotics versus OIT [31].

Omalizumab (Xolair, Genentech), a monoclonal anti-IgE antibody approved for treatment of asthma, has had success as an adjuvant to OIT. It reduces the concentration of circulating IgE and mast cell activation and potentially alleviates allergic reactions [32]. In 2013, Schneider et al. published a pilot study of omalizumab in high-risk peanut-allergic participants. Thirteen participants aged 7 to 15 years received omalizumab for 12 weeks prior to onset of OIT. A cumulative dose of 992 mg peanut flour (about 496 peanut protein; peanut flour contains about 50 % peanut protein) was administered over a period of 6 h during the rush desensitization. Updosing escalation phase began with 500 mg peanut flour the next day and increased gradually over time until the daily maintenance dose of 4,000 mg peanut flour was reached. Twelve weeks after omalizumab withdrawal, 92 % (12/13) tolerated oral food challenge with 8,000 mg peanut flour and achieved desensitization [33], indicating a rapid decrease in time to desensitization. A major limitation of the study was the small sample size and the absence of a placebo group. However, the data from the study provides preliminary evidence regarding the safety and efficacy of adjunct omalizumab. MacGinnitie et al. also reported in a phase 2 double-blind, placebo-controlled trial that omalizumab facilitates rapid oral desensitization. A total of 37 peanut-allergic participants aged 6–19 years were enrolled and randomized in a 3.5 : 1 ratio with 29 participants receiving omalizumab and 8 receiving placebo. OIT began 12 weeks after the first dose of omalizumab. Omalizumab was administered till week 19 to participants who tolerated 1625 mg peanut protein. There were 8 participants including 2 from active group and 6 from control who could not tolerate 250 mg of peanut protein after 8 weeks of desensitization, and thereby received open-label omalizumab, while initial therapy remained blinded. Daily maintenance dose was 2000 mg of peanut protein. Six weeks after withdrawal of omalizumab, 73.9 % of the omalizumab group, 12.5 % of the placebo group, and 100 % of the open-label group reached desensitization to 2,000 mg of peanut protein. Twelve weeks after withdrawal of omalizumab, 79 % of the active group and 12.5 % of the placebo group achieved desensitization to 4,000 mg of peanut protein [34]. These studies indicate that adjuvant omalizumab with OIT leads to faster desensitization as it allows participants to start at a higher initial dose than conventional OIT and

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reduces the number of allergen doses needed to reach the target maintenance dose.

Sublingual immunotherapy

SLIT is a well-studied method of immunotherapy in individuals with allergic rhinitis [20]. Allergens, in the form of drops or tablets are held under the tongue and the immunogenic properties of the oral mucosa are invoked, leading to desensitization over time [20]. The primary indication for SLIT continues to be allergic rhinoconjunctivitis; however, it is being actively explored in the treatment of FA [20, 35], and since the first reported trials in 2003 for FA to kiwi fruit [36], there have been many clinical trials showing promise for several foods, including peanut.

Since 2011, there have been two randomized, DBPCFC trials for peanut SLIT [37, 38]. The first study, by Kim et al. [37], enrolled 18 peanut-allergic children (ages 1–11 years) who were either randomized to peanut SLIT (n = 11) or placebo (n = 7). The dose of SLIT was kept under the tongue for 2 min and then swallowed. Over the next 6 months, during the escalation phase, the participants in the active group reached a dose of 2.5 mg of peanut protein and continued for an additional 6 months in the maintenance phase and then underwent DBPCFC. All 11 children in the active group were able to complete the desensitization protocol. The median dose of the posttreatment OFC was 1,710 mg, which was more than 20 times the amount achieved in the placebo group (85 mg). There were minimal safety concerns in the study with dosing side effects mainly involving oropharyngeal symptoms which generally did not require treatment.

Two years later, Fleischer et al. [38], published the results of the first multicenter, randomized, double-blind placebo-controlled clinical trial involving peanut SLIT. The study included 40 participants (ages 12–37 years), who were treated with peanut SLIT or placebo. Participants performed an initial peanut DBPCFC for inclusion in the study, with a median successfully consumed dose of 46 mg. At the end of phase 1 of the trial (44 weeks; goal dose of 1.386 mg peanut protein per day), 14 out of 20 (70 %) participants were considered "responders" and able to tolerate either 5,000 mg of peanut powder (about 2,500 mg of peanut protein) or a 10-fold higher amount than their baseline challenge. The median successfully tolerated dose increased from 3.5 to 496 mg. During the second phase of the study (unblinded), the active peanut-SLIT group continued on maintenance therapy for an additional 24 weeks (total 68 weeks), and the placebo group crossed over to a higher active peanut SLIT dose (3.696 mg of peanut protein daily). After 68 weeks of therapy, the median tolerated dose of peanut increased to 996 mg in the original active peanut-SLIT group. For the participants in the crossover group (original placebo group), who received 44 weeks of active peanut-SLIT, 7 of 16 participants (35 %) were considered to be "responders", and the median successfully consumed dose was up to 496 mg from a baseline of 21 mg. Based on these results, the authors concluded that the longer duration of treatment was more efficacious than the higher dose. The safety profile was again found to be very reassuring. Of the 10,855 peanut-SLIT doses over 44 weeks, 63.1 % of participants were symptom free. On excluding oropharyngeal symptoms, 95.2 % of participants were found to be symptom free [38].

The study continued for 3 additional years over an open-label period of active peanut SLIT along with yearly DBPCFCs. At 3 years, participants who passed DBPCFC to 10,000 mg (about 5,000 mg peanut protein) discontinued peanut maintenance doses and SU was assessed 8 weeks later by another DBPCFC to 10 g peanut powder and an open feeding of peanut butter. Only 4 of the original 40 participants (11%) achieved SU. There were no notable differences between the group on 1,386 vs. 3,695 mg of daily peanut protein. The safety profile was excellent; however the authors concluded that peanut SLIT induces only a modest level of desensitization [39].

Sublingual immunotherapy versus oral immunotherapy

Only one study to date has directly compared OIT and SLIT in a randomized double-blind placebo-controlled clinical trial while another study has performed a retrospective comparison. In 2013, Chin et al. performed a retrospective comparison of peanut OIT vs. SLIT using data from previous published SLIT and OIT protocols for peanut [23, 37]. In these studies, 27 subjects underwent peanut SLIT on a dose of 2 mg/day of peanut protein, and 18 subjects were treated with an OIT dose of 4,000 mg/day of peanut protein. DBPCFC were performed after 12 months of therapy to 2,500 mg in the SLIT group and 5,000 mg in the OIT group. Although there were differences among the DBPCFC protocols, participants in the SLIT group reacted at lower eliciting dose thresholds than the participants in the OIT group. Subjects in the OIT group were 3 times more likely to pass the 12-month DBPCFC than the subjects in the SLIT group. The authors concluded that OIT was more efficacious than SLIT in inducing desensitization to peanut protein.

Two years later, Narisety et al. published the results of a randomized double-blind, placebo controlled pilot study exploring the differences between SLIT and OIT for peanut allergy [40]. The study included 21 children (between 7–13 years) who were randomized to receive active SLIT vs placebo OIT

or active OIT vs. placebo SLIT. The doses were escalated to 3.7 mg in the SLIT group or 2,000 mg in the OIT group, and the participants were challenged after 6 and 12 months of treatment. After the 12-month challenge the participants were unblinded, therapy was modified and participants were offered an additional 16 months of therapy. The participants who passed OFCs at 12 or 18 months (for those with extended therapy), discontinued therapy for 4 weeks and were rechallenged. In all, 63.3 % of the participants in the active OIT group and 70 % in the active SLIT group completed the 12-month double-blind phase and had a greater than 10-fold increase in challenge threshold compared to baseline. However, the threshold was significantly larger in the OIT group (141-fold) vs. the SLIT group (22-fold). At the end of the study 1 participant from the SLIT group and 3 from the OIT group successfully demonstrated SU. OIT appeared to be far more efficacious than SLIT for the treatment of peanut allergy. Notably, adverse reactions were more common with OIT, including moderate reactions, doses requiring treatment and study discontinuation due to gastrointestinal symptoms.

Discussion

OIT is a well-investigated approach to treat FA and has been studied in many clinical trials for over a decade. More recently, studies using adjuvants such as omalizumab and probiotics with OIT have shown promise and appear to reduce the rate of recurrence of peanut sensitization after a period of peanut avoidance or elimination as well as the lengthy treatment period. Adjuvant omalizumab with OIT has also been shown to be safe and effective in those with multiple food allergies (including peanuts) [41]. Clinical evidence has been accumulated substantially more in OIT than in SLIT. Although there are a relatively fewer number of SLIT clinical trials targeting peanut allergy, the efficacy and safety of SLIT has been demonstrated in allergic rhinitis and other FA. It is not surprising to see that SLIT of which the treatment dose is log-fold lower than OIT, is associated with fewer adverse reactions and symptom-related early study withdrawal. Current evidence shows that significantly greater immunologic changes are seen in OIT than in SLIT, specifically, changes in skin test results, peanut-specific IgE, IgG4, and IgE/IgG4 ratio, and basophil activation. OIT tends to have a higher and less variable eliciting threshold in OFC than SLIT. It has been difficult to maintain SU after treatment in most participants with either modality. It is noteworthy that combination of the two modalities could induce significant increases in challenge thresholds and protection against adverse reactions. In its current state SLIT may be useful as a bridging technique before initiating OIT in highly sensitive individuals or it may be coupled with adjuvants to make it more effective and be used as stand-alone therapy.

Further investigation is needed to define the optimal dosing strategy and administration protocol in both approaches, and the potential for combination of the two treatment methods remains to be explored. More randomized, double-blinded, placebo-controlled, head-to-head clinical trials are necessary for a direct comparison. More data is needed for the long-term outcome as well, since very little is known about the effects of even brief lapses in exposures, after many years of therapy.

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Conflict of interest

W. Zhang, S.B. Sindher, V. Sampath and K. Nadeau declare that they have no competing interests.

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References

1. Savage J, Johns CB. Food allergy: epidemiology and natural history. Immunol Allergy Clin North Am 2015;35:45–59
2. Warren CM, Otto AK, Walkner MM, Gupta RS. Quality of life among food allergic patients and their caregivers. Curr Allergy Asthma Rep 2016;16:38
3. Gupta RS, Springston EE, Warrier MR, Smith B, Kumar R, Pongracic J, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. Pediatrics 2011;128:e9–e17
4. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL, et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4 year follow-up. J Allergy Clin Immunol 2017;140:145–153e8
5. Savage JH, Matsui EC, Skripak JM, Wood RA. The natural history of egg allergy. J Allergy Clin Immunol 2007;120:1413–7
6. Skripak JM, Matsui EC, Mudd K, Wood RA. The natural history of IgE-mediated cow's milk allergy. J Allergy Clin Immunol 2007;120:1172–7
7. Begin P, Paradis L, Paradis J, Picard M, Des Roches A. Natural resolution of peanut allergy: a 12-year longitudinal follow-up study. J Allergy Clin Immunol Pract 2013;1:528–530e1-4
8. Vander Leek TK, Liu AH, Stefanski K, Blacker B, Bock SA. The natural history of peanut allergy in young children and its association with serum peanut-specific IgE. J Pediatr 2000;137:749–55

9. Kostadinova AI, Willemsen LE, Knippels LM, Garssen J. Immunotherapy—risk/benefit in food allergy. Pediatr Allergy Immunol. 2013;24:633–44
10. Nelson HS, Lahr J, Rule R, Bock A, Leung D. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. J Allergy Clin Immunol 1997;99:744–51
11. Sampson HA, Shreffler WG, Yang WH, Sussman GL, Brown-Whitehorn TF, Nadeau KC, et al. Effect of varying doses of epicutaneous immunotherapy vs placebo on reaction to peanut protein exposure among patients with peanut sensitivity: a randomized clinical trial. JAMA 2017;318:1798–809
12. Nowak-Wegrzyn A, Fiocchi A. Is oral immunotherapy the cure for food allergies? Curr Opin Allergy Clin Immunol 2010;10:214–9
13. Rolinck-Werninghaus C, Staden U, Mehl A, Hamelmann E, Beyer K, Niggemann B. Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? Allergy 2005;60:1320–2
14. Hussey Freeland DM, Fan-Minogue H, Spergel JM, Chatila TA, Nadeau KC. Advances in food allergy oral immunotherapy: toward tolerance. Curr Opin Immunol 2016;42:119–23
15. Rachid R, Umetsu DT. Immunological mechanisms for desensitization and tolerance in food allergy. Semin Immunopathol 2012;34:689–702
16. Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. World Allergy Organ J 2015;8:17
17. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. J Allergy Clin Immunol 2014;133:621–31
18. Vickery BP, Scurlock AM, Jones SM, Burks AW. Mechanisms of immune tolerance relevant to food allergy. J Allergy Clin Immunol 2011;127:576–84. quiz 85–6
19. Yu W, Freeland DMH, Nadeau KC. Food allergy: immune mechanisms, diagnosis and immunotherapy. Nat Rev Immunol 2016;16:751–65
20. Jay DC, Nadeau KC. Immune mechanisms of sublingual immunotherapy. Curr Allergy Asthma Rep 2014;14:473
21. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol 2009;124:292–300, e1-97
22. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol 2009;124:286–91, 91 e1-6
23. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol 2011;127:654–60
24. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet 2014;383:1297–304
25. Kukkonen AK, Uotila R, Malmberg LP, Pelkonen AS, Makela MJ. Double-blind placebo-controlled challenge showed that peanut oral immunotherapy was effective for severe allergy without negative effects on airway inflammation. Acta Paediatr 2017;106:274–81
26. Vickery BP, Scurlock AM, Kulis M, Steele PH, Kamilaris J, Berglund JP, et al. Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy. J Allergy Clin Immunol 2014;133:468–75
27. Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol 2017;139:173–181e8
28. Nagakura KI, Sato S, Yanagida N, Nishino M, Asaumi T, Ogura K, et al. Oral immunotherapy in Japanese children with anaphylactic peanut allergy. Int Arch Allergy Immunol. 2018;175:181–8
29. Bird JA, Spergel JM, Jones SM, Rachid R, Assa'ad AH, Wang J, et al. Efficacy and safety of AR101 in oral immunotherapy for peanut allergy: results of ARC001, a randomized, double-blind, placebo-controlled phase 2 clinical trial. J Allergy Clin Immunol Pract 2018;6:476–485.e3
30. Tang ML, Ponsonby AL, Orsini F, Tey D, Robinson M, Su EL, et al. Administration of a probiotic with peanut oral immunotherapy: A randomized trial. J Allergy Clin Immunol 2015;135:737–744e8
31. Hsiao KC, Ponsonby AL, Axelrad C, Pitkin S, Tang MLK, Burks W, et al. Long-term clinical and immunological effects of probiotic and peanut oral immunotherapy after treatment cessation: 4 year follow-up of a randomised, double-blind, placebo-controlled trial. Lancet Child Adolesc Health 2017;1:97–105
32. Dantzer JA, Wood RA. The use of omalizumab in allergen immunotherapy. Clin Exp Allergy. 2018;48:232–40
33. Schneider LC, Rachid R, LeBovidge J, Blood E, Mittal M, Umetsu DT. A pilot study of omalizumab to facilitate rapid oral desensitization in high-risk peanut-allergic patients. J Allergy Clin Immunol 2013;132:1368–74
34. MacGinnitie AJ, Rachid R, Gragg H, Little SV, Lakin P, Cianferoni A, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. J Allergy Clin Immunol 2017;139:873–881e8
35. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol 2012;129:448–455, 55 e1-5
36. Mempel M, Rakoski J, Ring J, Ollert M. Severe anaphylaxis to kiwi fruit: Immunologic changes related to successful sublingual allergen immunotherapy. J Allergy Clin Immunol 2003;111:1406–9
37. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol 2011;127:640–646e1
38. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol 2013;131:119–127e1-7
39. Burks AW, Wood RA, Jones SM, Sicherer SH, Fleischer DM, Scurlock AM, et al. Sublingual immunotherapy for peanut allergy: long-term follow-up of a randomized multicenter trial. J Allergy Clin Immunol 2015;135:1240–1248.e1
40. Narisety SD, Frischmeyer-Guerrerio PA, Keet CA, Gorelik M, Schroeder J, Hamilton RG, et al. A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy. J Allergy Clin Immunol 2015;135:1275–1282e6
41. Andorf S, Purington N, Block WM, Long AJ, Tupa D, Brittain E, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. Lancet Gastroenterol Hepatol 2018;3:85–94
42. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol 2010;126:83–91e1
43. Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. Clin Exp Allergy 2011;41:1273–81
44. Chin SJ, Vickery BP, Kulis MD, Kim EH, Varshney P, Steele P, et al. Sublingual versus oral immunotherapy for peanut-allergic children: a retrospective comparison. J Allergy Clin Immunol 2013;132:476–478e2