

Oral and sublingual peanut immunotherapy is not ready for general use

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ABSTRACT

Food oral immunotherapy (OIT) is an investigational peanut allergy treatment aimed to achieve specific oral tolerance induction. Allergic children are given titrated oral (or sublingual) doses of their allergen on a daily basis, unlike in subcutaneous immunotherapy (SCIT). OIT is theorized to cause a shift from a Th2 to a Th1 regulatory environment, reflected by increases in food-specific IgG4/IgE, and the production of FoxP3. Peanut OIT holds special promise because peanut allergy has an unfavorable natural history and is rarely outgrown. A high percentage of the participants experience symptoms during peanut OIT, including anaphylaxis, warranting epinephrine and/or discontinuation of therapy. This is a concerning fact given that the studies have mostly targeted only older children, with less historical reactivity for enrollment. The handful of peanut OIT studies have shown that some participants can be desensitized to peanut, but none have shown that long-term tolerance can be reestablished. Factors predictive of which patients are most likely to succeed and become desensitized through OIT are unknown. Some private practices have begun offering peanut OIT as a therapy. Such practice is potentially dangerous given the safety and efficacy of OIT in randomized controlled clinical trials is still not well established. Therefore, until further investigation emerges that conclusively demonstrates OIT is safe, intermediate and long-term outcomes are better established, the number of participants that experience symptoms is reduced, and proof of concept established in patients of all ages, (irrespective of past reaction severity), OIT is not ready for use in the general allergy practice.

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Food allergy affects ~4–8% of U.S. children, and 90% of cases involve allergy to peanuts, tree nuts, milk, eggs, wheat, soy, fish, and shellfish. These allergies can be more severe with subsequent reexposure. With the case of peanuts, tree nuts, fish, and shellfish, these tend to be lifelong allergies, but milk, eggs, wheat, and soy are generally thought to be outgrown at some point in childhood. Beyond avoidance, there is no therapy.¹

Food oral immunotherapy (OIT) is a potential food allergy therapy.¹ In OIT, an allergic individual is slowly desensitized in stepwise fashion to their food allergen, through either an oral or sublingual route. After a rapid in-office desensitization, daily small doses of the allergen are administered at home, and the

dose is increased in the office approximately every 2 weeks.^{2,3} The goal of the therapy is to create a desensitized state, and then eventual lasting specific oral tolerance, through an immunologic shift decreasing the Th2 response and up-regulating the T-regulatory (Treg) environment.^{2–4}

Food OIT is an investigational, National Institutes of Health-funded therapy being researched at several academic medical centers in the United States and internationally. The research at U.S. institutions requires protocols in which the food item has been granted investigational new drug status, because food is used as a medical intervention.⁵ A number of private practices have also begun offering food OIT without seeking an investigational new drug, some under research protocols, but others as an office-based service.^{6–8} Nonresearch use of OIT has been met with criticism that the therapy is not ready for use in general practice.⁹ This article will focus on why peanut OIT, in particular, still is not ready for use outside of the research setting.

HOW DOES FOOD OIT WORK?

There are two potential effects of OIT: desensitization and tolerance. Desensitization implies a transient pro-

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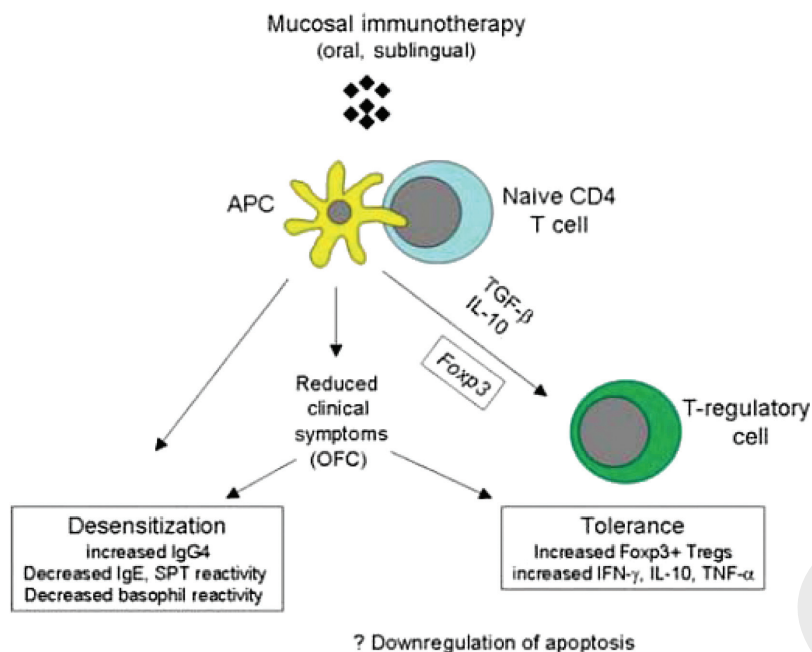


Figure 1. Theorized mechanism of how oral immunotherapy may work. Adapted, with permission, from Scurlock AM *et al.*²

tection from allergy achieved by rapidly overwhelming the IgE response through titrated allergen exposure but requires continual reexposure to the allergen to maintain this state. Desensitization induces IgG₄/IgE ratio shifting, and a decrease in mast cell/basophil activation.^{2,10} Tolerance, in contrast, infers *ad libitum* ability to consume the item without continuous reexposure, through modulation of the immune response from Th2 to Th1 through Treg cells to create a permanent state of anergy (Fig. 1). Peanut OIT strives to produce both effects, although the latter is the more immunologically desirable outcome. To date, only desensitization has been achieved for peanut OIT.³

DO THE DATA FROM OIT STUDIES CLEARLY SUPPORT ITS GENERAL USE?

To answer this question, rigorous review of the patient selection, study designs, outcomes, efficacy, and safety of the published studies is needed to determine the quality and weight of evidence. This review will focus primarily on the three U.S. trials, and two non-U.S. trials because these are the largest published studies.^{11–17} Table 1 details the protocols used in these studies and their key findings.

Is Patient Selection Adequate?

The completed OIT studies are essentially phase I/II investigations and have exclusively enrolled only older, less severely reactive, patients (except for the two non-U.S. studies).^{11,13–15,17} These studies showed proof of concept and baseline safety/efficacy. However, children with more severe reactivity, poorly controlled asthma, or age of <6 years have generally been excluded, which limits the extent to which the conclusions can be gener-

alized. Consecutive enrollment was only used by Anagnostou *et al.*, so the potential for selection bias in these studies is very high.¹⁷ More concerning is that only 2 of 5 studies confirmed the presence of peanut allergy with a preenrollment challenge.^{11,17} Challenge is necessary to ensure that already tolerant children are not enrolled, which would significantly bias the result. This would potentially necessitate challenge of children who may have very high peanut-specific IgE (sIgE), a group generally not challenged¹⁸ but which would presumably be good candidates for the therapy.

Another key limitation is that no efforts were made to correct for study-arm imbalance attributable to significant patient dropout. This is crucial because these are small studies that experienced dropout (or failure to complete) rates of 33% in the study by Blumchen *et al.*,¹¹ 25% in the study by Jones *et al.*,¹³ 4.5% in the study by Anagnostou *et al.*,¹⁷ and 15% in the study by Varshney *et al.*, in the treatment group,¹⁵ versus 0 in the placebo group. Without adjusting for differences between those that drop out versus those that remain in the trial, the validity of the findings becomes questionable. Furthermore, enrollment was not consecutive except for the Anagnostou *et al.* study,¹⁷ which creates vulnerability due to selection bias and the clustering effect of conducting these studies at large referral centers. The enrollees may not be representative of the typical peanut-allergic patient in the general population. Therefore, these results can not be generalized to the community level.

Were the Study Designs Adequate to Assess the Outcome?

The designs of these five studies were varied—three were open-label uncontrolled case series and two were

Table 1 Summary of findings from published studies of peanut OIT

	Jones <i>et al.</i> ¹³	Blumchen <i>et al.</i> ¹¹	Kim <i>et al.</i> ¹⁴	Varshney <i>et al.</i> ¹⁵	Anagnostou <i>et al.</i> ¹⁷	Gallucci <i>et al.</i> ⁶ / Wasseman <i>et al.</i> ⁷	Factor <i>et al.</i> ⁸
Type	Open, uncontrolled	Open, uncontrolled	Randomized double blind placebo controlled	Randomized double blind placebo controlled	Open (consecutive enrollment) and uncontrolled	Open and uncontrolled	Open and uncontrolled
<i>n</i>	39	23	18	28	22	40 (among 75 desensitized cases including milk, egg, and peanut, total no. of patients undergoing therapy was not reported)	93
Dropout	10	7	0	3 From intervention arm, 0 placebo	1	10 (not stratified for peanut specifically)	7
Vehicle	Peanut flour	Crushed peanut	Sublingual drops	Peanut flour	Peanut flour	Peanut flour	Peanut M&M
Pre-entry challenge required	No	Yes	No	No	yes	No	No (done in 1 patient failing other entry criteria)
Day 1 protocol	50 mg in office rapid desensitization target	7 Days inpatient rush desensitization to 500 mg	None: single 0.25- μ g dose administered	6 mg or appearance of first symptoms (minimum of 1.5 mg required)	None: Gradual build to 800 mg at 2 wk advancing intervals	Unspecified incremental amount given for total of 20–26 doses or reaction provoked	Start 0.1 mg, double dose q30 minute to 6 mg on day 1 (total of 12-mg cumulative dose)
Maintenance protocol	Build to 300 mg target through home dosing	Starting from 1/100 of eliciting dose in the challenge, build up to 2 g or highest dose that could be maintained without symptoms for 8 wk (500 mg minimum)	Slow desensitization to 2000- μ g target	Build to 4 g target	800 mg/day (or highest dose tolerated) maintained for 30 wk	Last tolerated dose maintained three times a day for 4 days, and then rechallenged in the office to the next dose increment	Build to target of 450 mg (3 peanut M&M), with 25–100% dose escalation based on prior dose tolerance

Table 1 Continued

	Jones <i>et al.</i> ¹³	Blumchen <i>et al.</i> ¹¹	Kim <i>et al.</i> ¹⁴	Varshney <i>et al.</i> ¹⁵	Anagnostou <i>et al.</i> ¹⁷	Gallucci <i>et al.</i> ^{6/} Wasserman <i>et al.</i> ⁷	Factor <i>et al.</i> ⁸
Dose escalation	Every 2 wk, in office	Increase dose by 20% every 2–4 wk, for up to 20 mo	Biweekly escalating doses in-office, every 2 wk for 6 mo	Every 2 wk for 44 wk	Dose approximately doubled from 0.5-mg start dose every 2 wk for 30 wk	Not reported	Every 2 wk, in office
Maintenance challenge	Challenge to 3.9 g peanut protein, and daily dose increased to 1.8 g after 12 mo of 300-mg daily dose	After tolerating highest attainable dose for 8 wk, dose discontinued 2 wk and subjects had DBPCFC to	After 6 mo of maintaining 2000- μ g dose, DBPCFC to 2.5 g peanut flower	After 4 wk of maintaining 4 g daily dose, DBPCFC to 5 g peanut flower	After completing 6 wk of maintenance therapy (challenged to 2.5 g protein)	Not reported	Not reported
Second maintenance challenge	None	None	None	None	After 30 wk (challenged to 6.6 g protein)	Not reported	Not reported
Challenge after discontinuation of therapy	No	Yes: 2-wk discontinuation period	No	No	No discontinuation	Not reported	Not reported
Rate of symptoms	93% in desensitization phase	7 Patients withdrew because of reactions; 7.9% rate of symptoms in rush phase (25/317 doses) and 2.6% rate of symptoms for full study (160/6137 doses)	11.5% SLIT group and 8.6% placebo group had symptoms (11/4182 doses required antihistamine)	47% of interventional arm in buildup (none in placebo); 1.4% of intervention arm build-up doses	86% Encountered symptoms; reported at patient level, not by dose	No peanut-specific events stratified; overall, 40/75 reacted ($n = 85$ total reactions)	40% with "adverse gastrointestinal effects... significant enough to warrant dose adjustments..." but not specifically described otherwise

Table 1 Continued

	Jones <i>et al.</i> ¹³	Blumchen <i>et al.</i> ¹¹	Kim <i>et al.</i> ¹⁴	Varshney <i>et al.</i> ¹⁵	Anagnostou <i>et al.</i> ¹⁷	Gallucci <i>et al.</i> ^{6/} Wasserman <i>et al.</i> ⁷	Factor <i>et al.</i> ⁸
Level of symptom reporting	Reported at the dose level	Reported at the dose level	Reported at the dose level	Reported at the dose level	Reported at the patient level	Reported at the patient level	Reported at the patient level
Efficacy	27/29 passed 3.9 g open challenge	11/14 Passed challenge at 2 wk to minimum of 500 mg of peanut; only 8 tolerated higher levels than baseline challenge	11/11 In interventional arm passed 1.71 g of peanut challenge vs 0 in placebo	16/19 In interventional arm tolerated 5 g challenge vs 0 in placebo	19/22 Tolerated up dosing to 800 mg/day of maintenance; 12/19 passed 6-wk challenge and 14/18 passed 30-wk challenge	Reported only on 40 successful cases; total number undergoing therapy not reported	90/100 Patients tolerated 450-mg (3 peanut M&M) maintenance dose; 3 additional patients were building to maintenance at time of publication
Biological markers	Decrease in peanut PST and sIgE, basophil activation; increase in IL-10 and FoxP3 in a subset of patients	Decreased IL-4 and IL-5 levels	Decreased peanut PST and sIgE; decreased basophil activation and lower IL-5	Decrease in PST, IL-5, and IL-13 in interventional group; increase in FoxP3 in interventional group	Decreased peanut PST and sIgE; noted lower peanut sIgE and Ara h 2 sIgE among those tolerating 30-wk challenge vs failing this challenge	None reported; 4 cases of EoE noted in the peanut OIT subjects	None
Epinephrine administration	5 (4 in desensitization, in in OFC)	None (8 had respiratory symptoms treated with β -agonist)	None	2 Interventional arm in build-up; 1 placebo in home dosing	None	22/85 Reported reactions (not stratified for peanut)	NA

OIT = oral immunotherapy; SLIT = sublingual immunotherapy; EoE = eosinophilic esophagitis; OFC = oral food challenge; DBPCFC = double blind, placebo-controlled food challenge; PST = prick skin test; sIgE = serum specific IgE.

placebo-controlled, randomized-controlled trials (one involving sublingual immunotherapy).^{5-11,13-15,17} The desensitization targets for day 1 also differed, and after the Jones *et al.*¹³ study the day 1 target was lowered in subsequent studies because of failure of many to achieve beyond a 12-mg dose target.¹⁵ The build-up and maintenance phases among the studies varied in duration, making comparison difficult. The Anagnostou *et al.* study did not use a rapid desensitization phase and instead used gradual up-dosing to maintenance.¹⁷ Blumchen *et al.* had deliberate interruption of therapy of 2 weeks to test tolerance, whereas the other four studies only tested the effect of desensitization.¹¹ Therefore, the results can not be pooled for analysis for a combined effect. A recent Cochrane review meta-analysis reached the same conclusion, noting only the Varshney study met adequate inclusion criteria for review.¹⁹

Four of the studies did have clearly delineated biological markers that were assessed. These involved measuring IgE/IgG4 ratio and pretherapy to post-therapy changes in the key cytokines IL-10, IL-5, IL-13, interferon- γ , and transforming growth factor β ; basophil reactivity; Treg cell numbers; end point titration of the skin test response; and OIT dose tolerance.^{13,15} However, these outcomes have differed by study, and in many cases they failed to reach statistical significance or were not powered to find a significant difference.¹⁵ The fifth study by Anagnostou *et al.* measured only the skin test and sIgE response and noted the same decrease in skin test and trend in reduction of sIgE.¹⁷ These are crucial limitations in understanding the molecular process responsible for how OIT works, a process still clearly under investigation.

Do the Results Clearly and Consistently Establish Safety?

A consistent conclusion of all five studies is that OIT is safe, based primarily on a low reported rate of adverse events. Adverse events were measured in four studies at the dose level, as a function of the total number of doses administered, a convention used in subcutaneous immunotherapy and other food OIT studies.¹¹⁻¹⁵ The Anagnostou *et al.* study denoted these at the patient level, however. Given the small numbers of patients in the study, if the event rate is analyzed at the patient level, using the actual number of patients as the denominator, a different picture emerges, and 26/29 in the Jones *et al.* study, 19/22 in the Anagnostou *et al.* study, and 9/19 in the treatment arm of the Varshney *et al.* trial had an adverse event.^{13,15} Data were not available for calculation in the Kim *et al.*¹⁴ and the Blumchen *et al.*¹¹ studies because the total numbers of patients reacting was not disclosed. Epinephrine was administered in three of the five studies during the

build-up and maintenance phases, including administration to patients at home.^{13,15} In the Blumchen study, although no epinephrine was administered, eight patients required a β -agonist for respiratory symptoms, which implies wheezing/lower respiratory symptoms.¹¹ In the United States, for sudden development of respiratory symptoms, most clinicians would administer epinephrine given the risk of impending anaphylaxis in this situation.^{11,20} There was no discussion as to why epinephrine was not used to treat these patients.

It was clearly reported that subjects dropped out of these studies because of reactions, and that reactions prevented patients from reaching the desensitization targets.^{13,14,17} That participants endured reactions, some severe, during the therapy is not problematic *per se*. This may ultimately prove to be a constraint of the therapy, as is the case in the building and maintenance phases of subcutaneous immunotherapy.²¹ However, these OIT reactions are problematic when occurring in subjects deliberately screened to have milder baseline allergy (except in the non-U.S. studies), which may have significant implications when broadening the therapy to those with more severe reactivity.^{11,17} At minimum, OIT requires more diligent study in patients with more robust ranges of reactivity, and factors predictive of successful therapy specific to baseline reactivity levels need to be identified. It is unclear if there is a ceiling effect for the efficacy of OIT based on the severity of one's historical reactivity. Furthermore, using the number of doses as the denominator in event reporting is somewhat misleading and may present conflicting meaning as to what "safe" implies.

Do the Results Clearly Establish Efficacy?

The data related to efficacy are consistent across the five studies and show that desensitization can be achieved in some, but not all, patients. Peanut skin tests, *in vitro* peanut-stimulated basophil reactivity, and peanut sIgE also consistently decreased among subjects receiving therapy. However, there was no consistent increased production of Treg's/FoxP3 or change in IL-10/transforming growth factor β /interferon- γ levels, key markers anticipated to be associated with a regaining of tolerance.¹¹⁻¹⁵ More practically, no minimum dose or duration of therapy necessary to produce desensitization is available, and there are no data pertaining to the long-term outcomes or adverse effects. One study showed short-term tolerance in a small number of participants after a 2-week discontinuation of therapy, although in this same study, several patients actually tolerated fewer peanuts after therapy than at baseline, which is clearly undesirable.¹¹ Anagnostou *et al.* did note lower baseline peanut sIgE and Ara h 2 sIgE among those passing maintenance chal-

lenge.¹⁵ Overall, there is poor understanding of how and in whom either tolerance or desensitization is most likely to occur, what the long-term outcomes may be, or if there is heterogeneity of treatment effect (e.g., do all patients receive equal benefit or do only certain subgroups receive equal benefit).²²

Importantly, the investigators have been very candid in reporting the limitations of their findings and proactive in addressing these issues. Several authors from the initial OIT studies have written a letter to the editor that disclosed many of the problems encountered in the course of study, such as reactions attributed to illness, menstruation, timing of the dose to a meal, and exercising.⁹

OIT OUTSIDE OF A RESEARCH CENTER

There are strong proponents that OIT is helpful and has sufficient proof of concept. Little is known about OIT use outside a research setting, however. Recently, Gallucci/Wasserman *et al.* described an OIT program in which 75 patients were desensitized to milk, eggs, and peanuts, of whom 40 completed peanut desensitization.^{6,7} Results were not stratified by allergen, but of 75 patients who completed therapy, 40 reacted, including 10 who withdrew, and 22 who required epinephrine. A total of 85 reactions were reported, 55 of which occurred in patients with peanut sIgE in excess of the 95% predictive decision point.^{6,7} Four cases of eosinophilic esophagitis within the peanut group were reported⁷ (EoE in milk but not peanut OIT has been reported in the academic studies).²³ Wasserman⁷/Gallucci⁶ *et al.* did not detail their specific protocol, patient selection criteria, or end points. Factor *et al.*⁸ desensitized 90/100 children to a target of 450 mg of peanuts (three peanut M & M's) using the Jones *et al.*¹³ protocol. Selection criteria were clearly detailed (Table 1). They reported significant gastrointestinal adverse events in 40/100 patients, and 7 dropped out.⁸ It is unclear how many other practices are providing OIT to patients, what the similarities are between protocols, or how these data compare with the academic medical center trials.

OVERALL ASSESSMENT

OIT is still an experimental food allergy therapy. The present data show desensitization is likely achievable in many subjects undergoing therapy, although not universally. The duration that the desensitization effect lasts or what the long-term implications of the therapy may be are unknown. There are no data that can forecast which patients undergoing OIT will attain success or develop complications such as EoE. Among the published data, there have been inconsistencies in the changes to key biomarkers that provide a mechanism to how OIT works. To date, exclusively older (>5 years

of age) and less severely reactive children have been included in the U.S. trials.

Many questions remain about the therapy's safety and efficacy. One could argue that the ongoing U.S. OIT studies are essentially phase I/IIa studies, in which proof of concept and understanding of the basic science involved in the response are being determined. However, these considerations are further proof of why peanut OIT should remain investigational, until these issues can be better clarified. The Cochrane review meta-analysis found only one study met review criteria and noted a high rate of adverse events in that trial that outweighed the present benefit the therapy could deliver, and can not be recommended, presently, as the National Institutes of Allergy and Infectious Diseases food allergy guidelines also specify.^{1,19}

Caution and restraint are warranted for those embarking on OIT in nonresearch settings. This is a yet-to-be-proven therapy, with questionable risk to benefit ratio, unclear safety, and unknown long-term outcomes. We should demand a higher burden of proof before OIT is deemed "ready," so that we can protect our patients from therapies that are still being investigated and optimized.

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