A randomized, double-blind, placebo-controlled pilot study of sublingual versus oral immunotherapy for the treatment of peanut allergy

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Background: Although promising results have emerged regarding oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) for the treatment of peanut allergy (PA), direct comparisons of these approaches are limited.
Objective: This study was conducted to compare the safety, efficacy, and mechanistic correlates of peanut OIT and SLIT.
Methods: In this double-blind study children with PA were randomized to receive active SLIT/placebo OIT or active OIT/placebo SLIT. Doses were escalated to 3.7 mg/d (SLIT) or 2000 mg/d (OIT), and subjects were rechallenged after 6 and 12 months of maintenance. After unblinding, therapy was modified per protocol to offer an additional 6 months of therapy. Subjects who passed challenges at 12 or 18 months were taken off treatment for 4 weeks and rechallenged.
Results: Twenty-one subjects aged 7 to 13 years were randomized. Five discontinued therapy during the blinded phase. Of the remaining 16, all had a greater than 10-fold increase in challenge threshold after 12 months. The increased threshold was significantly greater in the active OIT group (141- vs 22-fold, $P = .01$). Significant within-group changes in skin test results and peanut-specific IgE and IgG_4 levels were found, with overall greater effects with OIT. Adverse reactions were generally mild but more common with OIT ($P < .001$), including moderate reactions and doses requiring medication. Four subjects had sustained unresponsiveness at study completion.
Conclusion: OIT appeared far more effective than SLIT for the treatment of PA but was also associated with significantly more adverse reactions and early study withdrawal. Sustained unresponsiveness after 4 weeks of avoidance was seen in only a small minority of subjects. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Peanut allergy, food allergy, immunotherapy, sublingual immunotherapy, oral immunotherapy*

Peanut allergy (PA) is a common disease for which there is currently no effective treatment. Studies from the United States estimate an overall prevalence of up to 1.8% and suggest that this prevalence is increasing.[1-6] Treatment for PA currently relies on strict avoidance and ready access to self-injectable epinephrine. Accidental ingestions are unfortunately common,[7,8] and allergic reactions can be severe and life-threatening, with peanut allergies, tree nut allergies, or both accounting for the vast majority of fatal food-induced anaphylaxis.[9] Furthermore, only about 20% of children outgrow their PA.[10]

In recent years, promising studies have emerged regarding oral immunotherapy (OIT)[11-15] and sublingual immunotherapy (SLIT)[16,17] for the treatment of PA. Both modalities have been shown to induce desensitization, and some studies have demonstrated induction of sustained unresponsiveness in a subset of patients, especially with OIT. However, although OIT might be more effective, it also carries a higher risk of adverse reactions, presumably because of the higher doses used compared with SLIT. However, to date, there have been no prospective controlled studies comparing the 2 treatment modalities.

We conducted this randomized, double-blind, placebo-controlled pilot study to compare the safety and efficacy of SLIT and OIT in the treatment of children with PA to better understand the immunologic mechanisms underlying these treatments and their relationship to clinical outcomes. These mechanistic studies are provided in complete detail in the accompanying article by Gorelik et al.[18]

METHODS

Study objectives

The primary objective was to compare the capacity of peanut SLIT versus OIT to induce peanut desensitization, which was defined as a 10-fold increase in the oral food challenge (OFC) threshold after 12 months of therapy. Secondary objectives included the incidence of adverse events and changes in

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Abbreviations used
OFC: Oral food challenge
OIT: Oral immunotherapy
PA: Peanut allergy
SLIT: Sublingual immunotherapy
SPT: Skin prick test

mechanistic and other clinical outcomes. The protocol also included an assessment of sustained unresponsiveness, as determined by OFC after being off treatment for 4 weeks.

Subject selection

Subjects aged 6 to 21 years with a diagnosis of PA were recruited from the Johns Hopkins Pediatric Allergy Clinic. The study was approved by the Johns Hopkins institutional review board and the US Food and Drug Administration under an investigational new drug application. Inclusion criteria included a physician's diagnosis of PA, a positive peanut skin prick test (SPT) response (wheal response ≥3 mm larger than that elicited by the negative control), peanut-specific IgE levels of 0.35 kU_A/L or greater (ImmunoCAP FEIA; Thermo Fisher, Waltham, Mass), and a convincing reaction to a cumulative dose of 1000 mg or less of peanut protein in the baseline OFC (see Table E1 in this article's Online Repository at www.jacionline.org). Major exclusion criteria included a history of severe anaphylaxis to peanut with hypoxia, hypotension or neurologic compromise, reaction to placebo during the qualifying OFC, poorly controlled atopic dermatitis, poorly controlled asthma, severe persistent asthma (requiring >500 μg of fluticasone or its equivalent daily), and/or a diagnosis of eosinophilic esophagitis.

Study protocol

Study product. Treatments included peanut extract delivered by means of sublingual administration and peanut powder delivered by means of oral administration (Greer Laboratories, Lenoir, NC). The allergenic extract was prepared from the edible portion of peanut with 0.5% sodium chloride and 0.54% sodium bicarbonate as aqueous extracts in 50% glycerin. The peanut powder was also prepared from the edible portion of peanut, both ground and defatted. Placebo products included commercially obtained oat flour for OIT and glycerinated saline (Greer Laboratories) for SLIT.

Double-blind treatment phase. Participants underwent a baseline evaluation, including history, physical examination, skin testing, phlebotomy, and an OFC with up to 1000 mg of peanut protein, after which eligible subjects were randomized 1:1 to receive either active SLIT with placebo OIT or active OIT with placebo SLIT (see Fig E1 and see Tables E2 and E3 in this article's Online Repository at www.jacionline.org). Initial treatment doses were 0.000165 μg of peanut protein for SLIT and 0.1 mg for OIT, which were escalated on the first treatment day to 0.066 μg and 6 mg, respectively. Over the next 16 weeks, subjects took daily home doses of SLIT, followed by OIT, and returned every 1 to 2 weeks for observed dose increases, with goal maintenance doses of 3.7 mg/d (SLIT) and 2000 mg/d (OIT) of peanut protein. This dose was then taken daily for 12 months, with 10-g peanut protein OFCs conducted after 6 and 12 months of maintenance (see Table E1), after which subjects and investigators were unblinded. Subjects completing the 12-month OFC with no more than mild symptoms were taken off treatment for 4 weeks and rechallenged. All other subjects proceeded to the unblinded phase of the study.

Unblinded phase. Per protocol, subjects who reacted at the 12-month OFC were offered unblinded treatment for 6 additional months to assess the potential benefit of a longer course of therapy, the potential benefit of add-on therapy, and/or the possibility that prior treatment would reduce adverse reactions. Those who tolerated 5 to 10 g before reacting continued their prior treatment (SLIT or OIT) for 6 additional months, whereas those who reacted at less than 5 g continued their current treatment and had either active SLIT or OIT added. SLIT was added at the full 3.7-mg dose, whereas OIT was initiated at 10% of their final challenge dose and escalated to 2000 mg, after which 6 months of maintenance was completed. Subjects then underwent a 10-g OFC, and those who tolerated the OFC were taken off therapy for 4 weeks and rechallenged (see Fig E1).

Study procedures. The baseline OFC consisted of a cumulative dose of 1 g of peanut protein, with oat flour as a placebo. Subsequent challenges used a cumulative dose of 10 g. OFCs were double blind through the blinded phase of the protocol and then performed as open challenges. OFC results were considered positive with clear objective signs (eg, diffuse urticaria and wheezing) or convincing subjective symptoms (eg, severe persistent abdominal pain).

SPTs were performed at baseline and just before each OFC by using peanut extract (Greer Laboratories), serial 10-fold dilutions (1:20, 1:200, 1:2,000, 1:20,000, and 1:200,000 wt/vol) of peanut extract, and a panel of 9 other food and environmental allergens (soy, cashew, hazelnut, walnut, cat, dust mite, oak, ragweed, and timothy grass) using the GREER Pick device.

Laboratory studies included peanut-specific IgE and IgG_4 measurement, which was done before each OFC (ImmunoCAP). In addition, extensive mechanistic studies, as described in detail in the accompanying article,[18] were performed before each OFC, including spontaneous and stimulated basophil activity; allergen-induced cytokine expression in dendritic cell/T-cell cocultures, as determined by using multiplexing technology; and peanut-induced expression of MHC II and costimulatory molecules on dendritic cells, as determined by using flow cytometry.

Statistical analysis

Differences between SLIT and OIT for the primary outcome, a 10-fold increase in OFC threshold, were analyzed by using the Fisher exact test, and quantitative differences in the fold increase OFC threshold between the groups was evaluated by using the Mann-Whitney *U* test. Changes with treatment in OFC threshold, IgE and IgG_4 levels, and skin test results were analyzed by means of linear regression models with generalized estimating equations to account for repeated measures over time with robust SEs. Analysis of skin test responses to nonpeanut allergens included only those subjects with positive test results at baseline. Specific IgE and IgG_4 levels were log-transformed for analysis. Outcomes were analyzed by using both a per-protocol analysis, which did not include dropouts, and an intent-to-treat model, which considered dropouts to have the same OFC result on subsequent challenges as at baseline. Binary outcomes were evaluated by using χ^2 or Fisher exact tests, as appropriate, including percentage of doses with symptoms during treatment.

RESULTS

Study participants

Twenty-one subjects aged 7 to 13 years were randomized, including 10 in the active SLIT/placebo OIT group and 11 in the active OIT/placebo SLIT group (Fig 1). There were no significant differences between the 2 groups with regard to age, peanut-specific IgE levels (median, 163 vs 169 kU/L), peanut-specific IgG_4 levels, peanut SPT or end point SPT responses, or baseline OFC results (median cumulative dose, 21 mg for both groups; Table I).

Dose escalation and build-up

On initial dose escalation, all 10 subjects in the active SLIT group escalated to the maximum dose of 0.066 μg, whereas only 5 of 11 in the active OIT group reached the maximum dose of 6 mg. Of the remaining 6, one reached 1.5 mg, 2 reached 2.5 mg, 2 reached 3.5 mg, and 1 reached 5 mg. Twenty subjects completed the 16-week dose build-up phase and continued to maintenance dosing. One subject from the OIT group withdrew from the study after dose escalation because of a diagnosis of eosinophilic

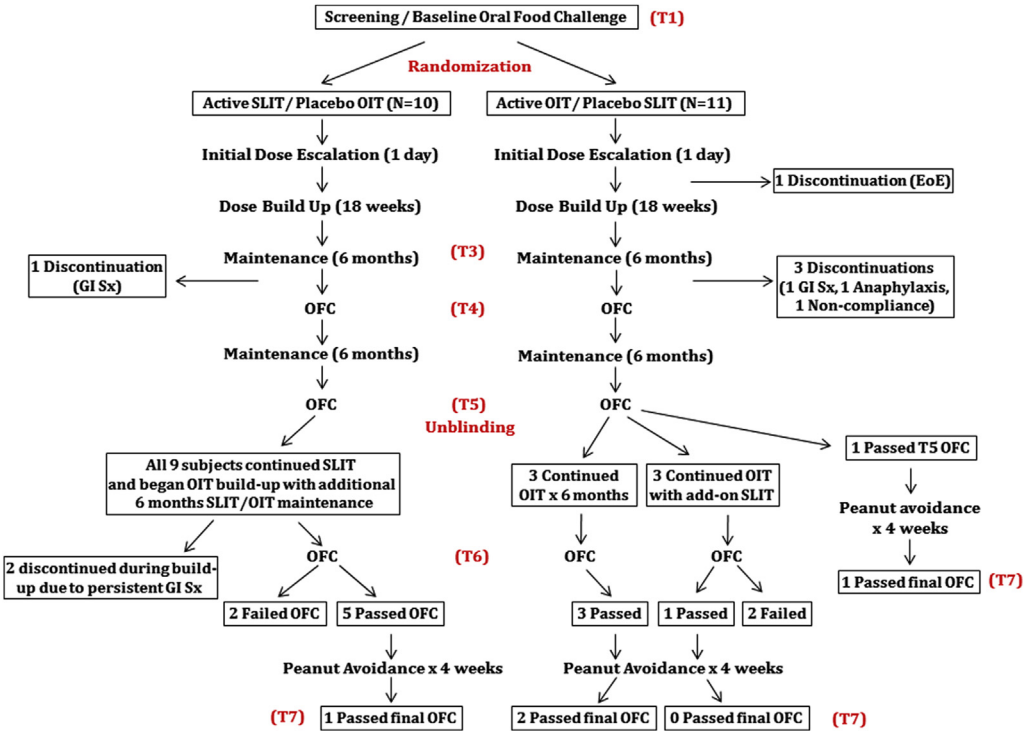

FIG 1. CONSORT diagram. Time points include T1 (baseline), T3 (end of dose build-up), T4 and T5 (after 6 and 12 months of maintenance, subjects unblinded at T5), T6 (completion of additional 6 months of maintenance), and T7 (4 weeks off therapy).

TABLE I. Subjects' demographics

	Active OIT/placebo SLIT	Active SLIT/placebo OIT
Total subjects (no.)	11	10
Age (y), median (range)	11.1 (9.7-13)	11.1 (7.2-12.4)
Sex (male)	7 (64%)	4 (40%)
Prior history of peanut anaphylaxis (no. of subjects)	6	1
Other food allergies (no. of subjects)	10	10
Atopic dermatitis (no. of subjects)	6	6
Asthma (no. of subjects)	9	4
Allergic rhinitis (no. of subjects)	10	9
Peanut IgE (kU_A/L), median (range)	169 (35.1-716)	163 (37.5-746)
Peanut skin test (mm), median (range)	12 (7.5-19)	9.3 (6.5-22)
Peanut end point SPT average wheal size (mm), median (range)	5.8 (4.2-8.6)	4.8 (1.3-8.9)
Cumulative threshold baseline DBPCFC (mg), median (range)	21 (6-146)	21 (1-146)

There were no significant baseline differences between the groups.
DBPCFC, Double-blind, placebo-controlled food challenge.

esophagitis, which was determined to be unrelated to the study given that it occurred after just 1 day of dosing and did not resolve after 12 weeks of peanut avoidance.

Maintenance therapy

Sixteen subjects (9 in the active SLIT and 7 in the active OIT groups) were able to complete therapy and undergo both OFCs after 6 and 12 months of maintenance. One subject receiving active SLIT discontinued because of persistent gastrointestinal symptoms, whereas 3 receiving active OIT discontinued: 1 with persistent gastrointestinal symptoms, 1 after a systemic reaction with home dosing, and 1 because of noncompliance.

OFC results

All 16 subjects who completed OFCs after maintenance had increases in their cumulative challenge thresholds compared with baseline values (Fig 2). Seven of 10 of the original active SLIT group and 7 of 11 of the active OIT group achieved the primary end point of a 10-fold increase compared with baseline values ($P = .76$ between groups). In the 9 subjects receiving SLIT, the median cumulative dose increased from a baseline of 21 mg (range, 1-146 mg) to 496 mg (range, 146-3,246 mg) after 6 months ($P = .01$) and 496 mg (range, 71-3,246 mg) after 12 months ($P = .02$). In the 7 subjects in the OIT group completing maintenance, threshold doses increased from 21 mg (range, 6-146 mg) to 7,246 mg (range, 146-10,000 mg) after 6 months ($P < .001$) and 7,246 mg (range, 146-10,000 mg) after 12 months ($P < .001$).

Between groups, the increase in the median challenge dose after 6 months (active SLIT, 14-fold; active OIT, 141-fold) and 12 months (active SLIT, 22-fold; active OIT, 141-fold) was significantly greater with OIT ($P = .009$ and $P = .01$). There were no substantial differences in results when an intent-to-treat analysis was used (data not shown).

Unblinded phase

Per protocol, each subject's treatment was potentially extended or adjusted based on the 12-month OFC outcome. All 9 subjects in the active SLIT group continued on SLIT and had active OIT

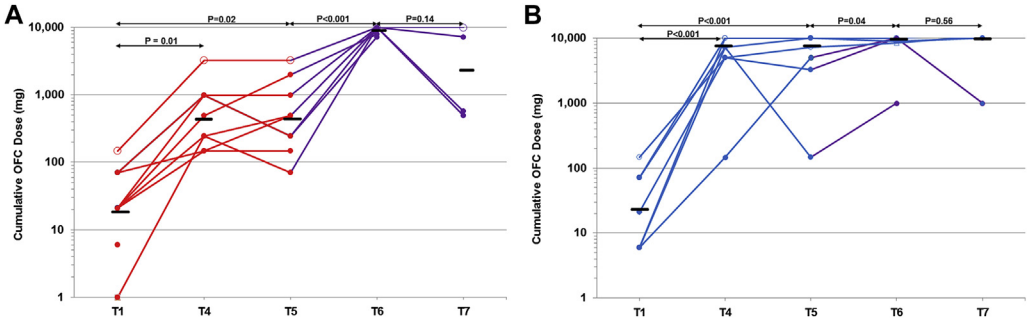

FIG 2. Change in cumulative OFC dose after SLIT **(A)** and OIT **(B)**. *Red lines* indicate active SLIT, *blue lines* indicate active OIT, and *purple lines* represent combined SLIT and OIT after unblinding. *Open circles* represent subjects with sustained unresponsiveness. Between groups, there were significantly greater changes in OFC thresholds with OIT compared with SLIT ($P = .008$ and $P = .01$ after 6 and 12 months of maintenance).

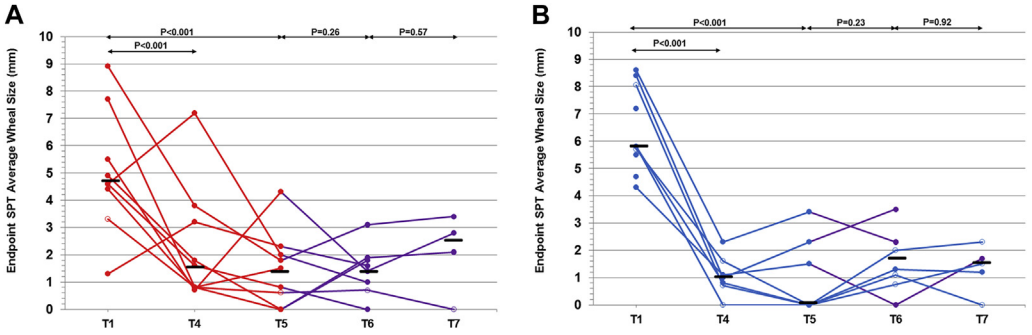

FIG 3. Change in end point skin test results after SLIT **(A)** and OIT **(B)**. *Red lines* indicate active SLIT, *blue lines* indicate active OIT, and *purple lines* represent combined SLIT and OIT after unblinding. *Open circles* represent subjects with sustained unresponsiveness. Comparison of the SLIT and OIT groups revealed similar changes in skin test results over time, with the exception of greater changes in the OIT group at T4 ($P = .03$).

added, of whom 2 were unable to complete the OIT build-up because of persistent gastrointestinal symptoms. The other 7 achieved active OIT maintenance and were rechallenged after 6 months, with a median OFC dose of 10,000 mg (range, 6,000-10,000 mg; $P < .0001$ compared with OFC after 12 months of SLIT alone). From the original active OIT group, 1 subject passed his OFC at the end of the blinded phase and was taken off treatment for 4 weeks and rechallenged, 3 extended their OIT for 6 months (all tolerating 10,000 mg in their end-of-treatment OFC), and the other 3 continued OIT and added active SLIT for 6 months before being rechallenged (median OFC cumulative dose, 10,000 mg; range, 996-10,000 mg; $P = .08$ compared with OFC after 12 months of OIT alone).

Transient versus sustained desensitization

As noted, 1 subject from the active OIT group passed his OFC on completion of the blinded phase. After 4 weeks off treatment, he tolerated the full challenge with only mild oropharyngeal and skin symptoms and successfully added peanut to his diet. Five of the 7 subjects from the active SLIT group who completed the 6 months of add-on OIT passed their end-of-treatment OFC, and on rechallenge, their median cumulative dose was 7,246 mg (range, 496-10,000 mg), with only 1 passing the challenge. In the other 4, 2 reacted at 496 mg, 1 reacted at 7,246 mg, and 1 reacted at 8,000 mg. Of the 6 subjects from the active OIT group, 4 were eligible for sustained unresponsiveness challenges, including one from the add-on SLIT group who reacted at 996 mg and 2 with no add-on therapy who passed the final challenge. Therefore in the final analysis 1 of 10 subjects originally assigned to SLIT and 3 of 11 subjects assigned to OIT had sustained unresponsiveness ($P = .59$).

Skin test results

SPT responses with full-strength peanut extract decreased in both groups through the blinded phase (SLIT: baseline median wheal, 9.3 mm; 5.5 mm after 6 months [$P = .10$] and 12 months [$P = .047$] of maintenance; OIT: baseline median wheal, 12 mm; 4.5 mm after 6 months [$P < .001$] and 0 mm after 12 months [$P < .001$]). With regard to end point SPTs, the average wheal size for the 5 concentrations of peanut decreased significantly in both groups (Fig 3). For the SLIT group, the median average wheal size decreased from 4.75 mm at baseline to 1.6 mm at 6 months ($P = .004$) and 1.5 mm at 12 months ($P < .001$). For the OIT group, the median average wheal size decreased from 5.8 mm at baseline to 1 mm after 6 months and 0 mm after 12 months ($P < .001$ for both).

Comparison of the SLIT and OIT groups revealed similar changes in SPT responses over time, with the exception of greater changes in the OIT group at T4 for both the full-strength and end point SPTs ($P = .01$ and .03, respectively) and for full-strength

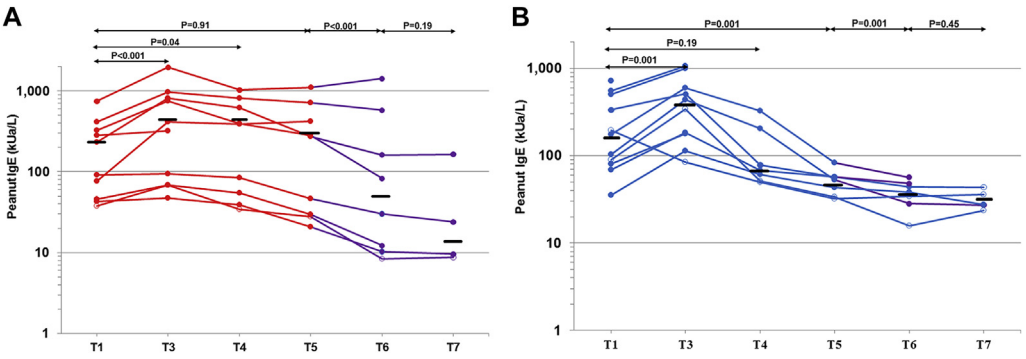

FIG 4. Change in peanut-specific IgE levels after SLIT **(A)** and OIT **(B)**. *Red lines* indicate active SLIT, *blue lines* indicate active OIT, and *purple lines* represent combined SLIT and OIT after unblinding. *Open circles* represent subjects with sustained unresponsiveness. By 6 months, the decrease in peanut IgE levels was greater in the OIT group, and this difference widened by 12 months ($P = .07$ and $P = .007$, respectively).

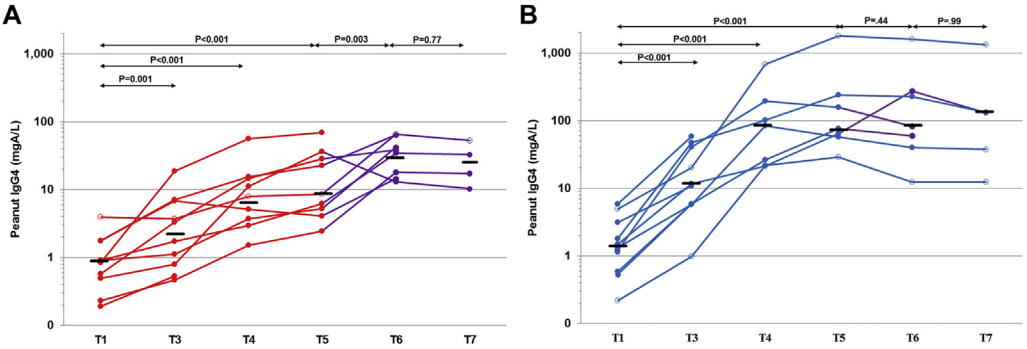

FIG 5. Change in peanut-specific IgG_4 levels after SLIT **(A)** and OIT **(B)**. *Red lines* indicate active SLIT, *blue lines* indicate active OIT, and *purple lines* represent combined SLIT and OIT after unblinding. *Open circles* represent subjects with sustained unresponsiveness. Between groups, there was overall a greater change from baseline in peanut-specific IgG_4 levels over time in the OIT group compared with the SLIT group at all time points (end of dose build-up [$P = .003$] after 6 and 12 months of maintenance [$P < .001$]).

SPTs at T5 ($P = .03$). There were no significant changes in skin test responses in the unblinded phase, including the addition of OIT to SLIT.

SPTs were also performed to 9 environmental and nonpeanut food antigens to assess for possible nonspecific treatment effects (see Fig E2 and see Table E4 in this article's Online Repository at www.jacionline.org). At baseline, positive SPT responses were found to soy in 5, cashew in 9, hazelnut in 10, walnut in 6, cat in 13, dust mite in 6, oak in 12, ragweed in 7, and timothy grass in 9. Significant changes in SPT wheal sizes were seen for several allergens, especially in the OIT group. Although no consistent pattern was evident, with apparent effects on both food and environmental allergens, many of these changes occurred early in treatment and disappeared later in the study.

Serologic outcomes

Peanut-specific IgE levels increased initially and subsequently decreased over time for both groups (Fig 4). For the SLIT group, the median increased from 163 kU_A/L (range, 37.5-746 kU_A/L) at baseline to 369 kU_A/L (range, 47.4-1960 kU_A/L) by the end of dose build-up ($P < .001$), remained higher after 6 months of maintenance (median, 387 kU_A/L; $P = .04$), and was not different from baseline after 12 months of maintenance (median, 273 kU_A/L; $P = .91$). In the OIT group the median increased from 169 kU_A/L (range, 35.1-716 kU_A/L) at baseline to 392 kU_A/L (range, 84-1069 kU_A/L) by the end of dose build-up ($P = .001$), after which medians decreased to 68 and 53 kU_A/L after 6 and 12 months ($P = .19$ and $<.001$ compared with baseline, respectively). Between groups, decreases in peanut IgE levels were greater in the OIT group at 6 and 12 months ($P = .07$ and $P = .007$). Further decreases in peanut IgE levels occurred in both groups during unblinded treatment.

Peanut-specific IgG_4 levels increased in both groups over the study (Fig 5). For the SLIT group, median levels increased from 0.9 mg_A/L at baseline to 2.5 mg_A/L at the end of dose build-up ($P = .001$), 7.9 mg_A/L after 6 months ($P < .001$), and 8.5 mg_A/L after 12 months ($P < .001$). For the OIT group, median levels increased from 1.3 mg_A/L at baseline to 11.3 mg_A/L at the end of dose build-up ($P < .001$), 83.4 mg_A/L after 6 months ($P < .001$), and 76 mg_A/L after 12 months ($P < .001$). Between groups, there was overall a greater change from baseline in the OIT group (end of dose build-up [$P = .003$] and after 6 and 12 months [$P < .001$]). In the unblinded phase the addition of OIT to SLIT resulted in a further increases in peanut IgG_4 levels ($P = .003$).

Correlation of laboratory and clinical outcomes

Subjects who had sustained unresponsiveness had lower peanut IgE levels at baseline (median, 79 vs 257 kU_A/L; $P = .02$) and

TABLE II. Blinded phase: summary of adverse events

Treatment group	Total doses (no.)	Doses with symptoms (%)	Type of symptoms (% of doses)				Severity (% of doses)		Treatment (% of doses)	
			Oral/pharyngeal	Skin	Respiratory	GI	Mild	Moderate	Antihistamines	β_2-Agonists
Active SLIT/Placebo OIT	4578	9.0	3.9	1.4	0.6	3.2	7.7	1.3	23.1	0.3
Dose escalation	100	6.0	3.0	2.0	1.0	0.0	6.0	0.0	0.0	0.0
Dose build-up	1336	18.2	9.9	1.9	1.2	5.2	17.1	1.1	19.8	1.1
Maintenance	3142	5.2	1.3	1.2	0.3	2.4	3.8	1.4	25.3	0.0
Active OIT/placebo SLIT	4049	42.8	24.2	2.8	6.9	9.0	39.4	3.4	40.9	1.9
Dose escalation	95	49.5	27.4	2.1	9.5	10.5	49.5	0.0	5.3	0.0
Dose build-up	1507	57.9	31.3	1.6	8.6	16.5	54.9	3.0	44.4	1.0
Maintenance	2447	33.3	19.6	3.6	5.7	4.3	29.5	3.8	40.2	2.5

GI, Gastrointestinal.

TABLE III. Unblinded phase: summary of adverse events

Treatment group	Total doses (no.)	Doses with symptoms (%)	Type of symptoms (% of doses)				Severity (% of doses)		Treatment (% of doses)	
			Oral/pharyngeal	Skin	Respiratory	GI	Mild	Moderate	Antihistamines	β_2-Agonists
Active SLIT + OIT	2599	5.1	1.8	0.5	0.5	2.4	3.7	1.4	1.4	0.2
Dose build-up	89	15.7	9.0	0.00	1.1	5.6	14.6	1.1	3.4	0
Maintenance	2510	4.7	1.6	0.5	0.4	2.3	3.3	1.4	1.3	0.2
Active OIT + SLIT	501	35.3	6.8	9.6	16.8	2.2	28.5	6.8	22.8	7.4
Active OIT	539	36.7	36.4	0.2	0.2	0.00	36.4	0.4	0.4	0.4

GI, Gastrointestinal.

greater decreases in IgE levels at T4 ($P = .02$). There were no significant relationships between OFC outcomes and baseline SPT results, end point SPT results, peanut IgG_4 levels, or changes in these measures over time. Detailed mechanistic assessments and their relationship to the clinical outcomes are provided in the accompanying article.[18]

Adverse reactions with dosing

In the blinded phase a total of 4578 doses were taken by the SLIT group, and 4049 doses were taken by the OIT group (Table II). Overall, the proportion of doses with adverse reactions was significantly higher in the OIT group (43% vs 9% of doses, $P < .001$). Most reactions were mild, although a small percentage were moderate in severity (3.4% vs 1.3%, $P < .001$). With regard to specific symptoms, all were more common in the subjects receiving OIT (eg, oral/pharyngeal symptoms, 24.2% vs 3.9%; respiratory symptoms, 6.9% vs 0.6%; and gastrointestinal symptoms, 9.0% vs 3.2%; $P < .001$ for all). When adverse reactions were assessed per subject, 9 of 10 in the SLIT group and 10 of 10 in the OIT group had symptoms with dosing ($P = 1.0$), with medians of 29 and 149 doses with symptoms ($P = .008$).

Antihistamines were used to treat symptoms with 40.9% of OIT doses versus 23.1% of SLIT doses ($P < .001$). This significant difference was present through all 3 phases of the blinded study. β_2-Agonists were also used for a significantly higher percentage of doses in the OIT group (1.9% vs 0.3%, $P < .001$). Five doses of epinephrine were required to treat systemic reactions in 4 subjects in the active OIT group: 1 during dose build-up and 4 during maintenance.

In the unblinded phase symptoms were experienced at a rate of 5.1% of 2599 total doses taken by the active SLIT/active OIT add-on group, 35.3% of 501 doses by the active OIT/active SLIT add-on group, and 36.7% of 539 doses by the active OIT–only group (Table III). Antihistamines were used for 1.4%, 22.3%, and 0.4% of doses, whereas β_2-agonists were used for 0.2%, 7.4%, and 0.4% of doses. Injectable epinephrine was required by 1 subject in the active SLIT/active OIT add-on group during the OIT build-up and in 1 subject in the active OIT/active SLIT add-on group during maintenance.

DISCUSSION

This is the first study to compare the safety and efficacy of OIT and SLIT for peanut or other food allergies in a double-blind, placebo-controlled trial. Given that prior food immunotherapy studies have been difficult to compare because of the differences in the doses and protocols used, we based our dosing on published protocols from the Consortium of Food Allergy Research (SLIT)[17] and Jones and Burks (OIT).[12-14] Although the study is limited by a small sample size and a high dropout rate, our results are consistent with the findings of previous studies, in which subjects in both groups were at least partially desensitized, as evidenced by 10-fold or greater increases in peanut challenge thresholds compared with baseline. However, the degree of desensitization was far greater in those receiving OIT compared with those receiving SLIT, with subjects tolerating an average of approximately 24 peanuts compared with 1 to 2 peanuts. This is similar to results of the Consortium of Food Allergy Research peanut SLIT study, in which most subjects increased their OFC threshold at least 10-fold but none reached the maximum OFC dose of 5 g and SLIT overall was not significantly superior to placebo with regard to changes in oral challenge thresholds.[17] In the end, only subjects who received OIT passed the full 10-g challenge and had the opportunity to be assessed for sustained unresponsiveness.

However, although the potential benefit of OIT appears far greater than that afforded by SLIT, the differences in safety between the 2 modalities are also striking, with nearly 4 times as many OIT doses causing symptoms. Although the majority of reactions were mild, moderate reactions were more common in the OIT group, as were the proportion of reactions requiring treatment with antihistamines, β_2-agonists, or injectable epinephrine. Furthermore, OIT was associated with a far greater number of treatment withdrawals because of intolerable symptoms. These results are overall similar to our recent open-label study comparing SLIT with OIT in children with milk allergy, in which we found far greater efficacy of OIT at the price of higher rates of adverse reactions,[19] as well as a retrospective comparison of peanut OIT and SLIT.[20]

Per protocol, treatment was modified after unblinding based on the outcome of each subject's OFC. On the basis of this design, all subjects receiving active SLIT had active OIT added for an additional 6 months of maintenance. Although the group is too small to draw any firm conclusions, 3 important themes emerge: (1) adding OIT to SLIT led to significant increases in challenge thresholds; (2) pretreatment with SLIT appeared to provide substantial protection against adverse reactions; and (3) although the protection from adverse reactions appeared quite dramatic overall, 2 of 9 still dropped out during OIT build-up because of intolerable persistent abdominal pain.

One of the most important issues in the development of immunotherapy for the treatment of food allergy relates to the potential to induce longer-term protection, referred to as sustained unresponsiveness, versus short-term desensitization. The initial blinded protocol did not address this question because only 1 subject (receiving OIT) was eligible for assessment of sustained unresponsiveness. This is not surprising because SLIT appears unlikely to induce that degree of desensitization, and even with OIT, this short course of treatment might not be adequate to induce complete desensitization, much less tolerance. However, continued treatment during the unblinded phase, especially adding OIT to SLIT, allowed for a test of sustained unresponsiveness in a total of 10 subjects, with 4 still tolerating the 10-g challenge after 4 weeks of avoidance. These results are overall similar to those reported in prior OIT studies to peanut, milk, and egg,[19,21,22] and it is clearly possible that more participants would have lost protection if the period of avoidance was extended beyond 4 weeks.

As the field of food immunotherapy moves forward, biomarkers that might predict response, adverse reactions, and/or the need to individualize dosing would be of great value. Consistent with prior studies,[12,15-17] both SLIT and OIT induced significant changes in skin test results, as well as peanut-specific IgE and IgG_4 levels. Although OIT did induce somewhat greater changes in each of these parameters and we found that a lower baseline peanut IgE level was associated with sustained unresponsiveness, we did not identify any biomarkers that were reliable predictors of any clinical outcome on an individual basis.

Finally, we assessed the possibility that there might be nonspecific effects of peanut immunotherapy using sequential skin testing to other food and environmental allergens. Although these data are limited by the fact that not all subjects were sensitized to these allergens, as well as by the high dropout rate, the results did suggest that peanut immunotherapy induced reduced skin test reactivity to both food and inhalant allergens, especially early in the course of OIT. Furthermore, the data suggest these changes were transient for many allergens, actually reverting toward baseline over the course of treatment. For example, 4 of 5 subjects receiving OIT who were sensitized to cat at baseline had no skin test reactivity after 6 months, although all had returned to baseline values by the end of treatment. The reasons for these findings are not clear but are especially interesting given the results in the accompanying mechanistic article, demonstrating that the immunologic effects of immunotherapy might be both transient and nonspecific.

In conclusion, in this randomized, double-blind comparison of peanut SLIT and OIT, OIT appeared considerably more robust with regard to clinical outcomes, laboratory parameters, and, unfortunately, adverse effects, including a high rate of dropouts because of adverse reactions. Although pretreatment with SLIT before OIT led to a dramatic reduction in overall adverse events, it did not eliminate the risk of intolerable gastrointestinal symptoms, leading to the discontinuation of therapy. Therefore although this study provides further support for the development of OIT for clinical use, it also clearly underscores the need for additional research to develop approaches that will maximize both efficacy and tolerability, potentially including longer periods of maintenance dosing and the study of younger children, as well as the potential use of adjuvants, modified allergens, or both.

Clinical implications: This comparison of peanut OIT and SLIT demonstrates far greater efficacy with OIT, although at the price of increased adverse reactions. Sustained unresponsiveness was only demonstrated in a small minority of subjects.

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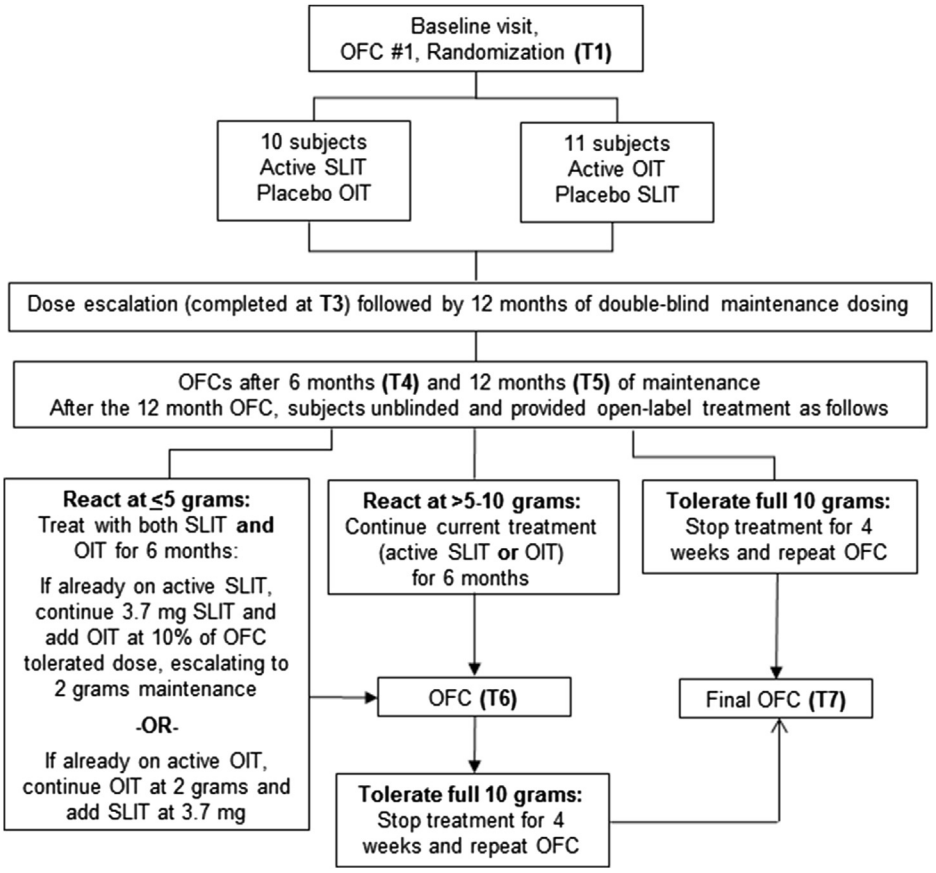

FIG E1. Study schematic indicating treatment groups and assignment of open-label treatment after the 12-month OFC.

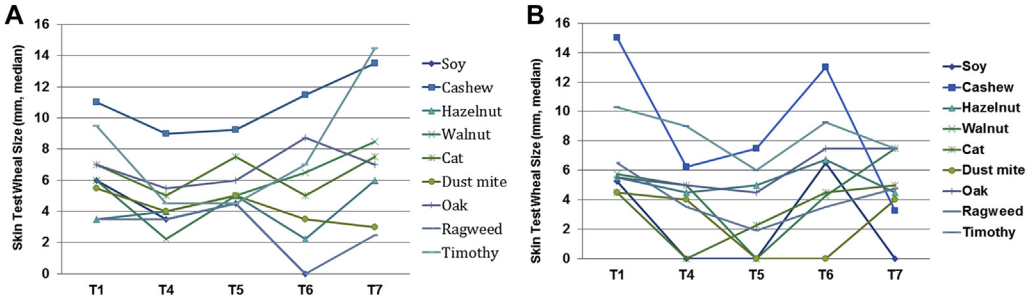

FIG E2. Change in SPT responses (median wheal size) for other food and environmental allergens after SLIT **(A)** and OIT **(B)**. See Table E4 for *P* values for the individual allergens at each time point.

TABLE E1. Peanut oral challenge dosing

Dose no.	Dose (mg)	Cumulative dose (mg)
Baseline challenge		
1	1	1
2	5	6
3	15	21
4	50	71
5	75	146
6	100	246
7	250	496
8	500	996
Posttreatment challenges		
1	1	1
2	5	6
3	15	21
4	50	71
5	75	146
6	100	246
7	250	496
8	500	996
9	1000	1996
10	1250	3246
11	1750	4996
12	2250	7246
13	2750	9996

TABLE E2. Peanut SLIT dosing

Dose no.	Visit (wk)	SLIT dose (μg)	Cumulative dose (μg)	Increase (%)
Dose escalation				
1	4 (2)	0.000165	0.000165	
2	4 (2)	0.00033	0.000495	100
3	4 (2)	0.00066	0.001155	100
4	4 (2)	0.00165	0.002805	150
5	4 (2)	0.0033	0.006105	100
6	4 (2)	0.0066	0.012705	100
7	4 (2)	0.0165	0.029205	150
8	4 (2)	0.033	0.062205	100
9	4 (2)	0.066	0.128205	100
Dose build-up: Phase I				
10	6 (4)	0.165	0.495	150
11		0.33		100
12	7 (6)	0.66	2.31	100
13		1.65		150
14	8 (8)	3.3	9.9	100
15		6.6		100
Dose build-up: Phase II				
16	9 (10)	16.5		150
17	10 (11)	33		100
18	11 (12)	66		100
19	**12 (13)**	**165**		**150**
20	13 (14)	330		100
21	14 (15)	660		100
22	15 (16)	1386		110
23	16 (17)	2310		67
24	17 (18)	3696		60

Boldface items signify the minimum tolerated dose required. Doses greater than 560 μL can be split into 2 doses. Standard concentration is 3300 μg of peanut protein/mL; 50 μL = 165 μg of peanut protein.

TABLE E3. Peanut OIT dosing

Dose no.	Visit (wk)	OIT dose (mg)	Cumulative dose (mg)	Increase (%)
Dose escalation				
1	4 (2)	0.1	0.1	
2	4 (2)	0.2	0.3	100
3	4 (2)	0.4	0.7	100
4	4 (2)	0.8	1.5	100
5	**4 (2)**	**1.5**	**3**	**88**
6	4 (2)	2.5	5.5	67
7	4 (2)	3.5	9	40
8	4 (2)	5	14	43
9	4 (2)	6	20	20
Dose build-up: Phase I				
10	6 (4)	12		100
11	7 (6)	24		100
12	8 (8)	48		100
Dose build-up: Phase II				
13	9 (10)	75		56
14	10 (11)	115		53
15	11 (12)	170		48
16	**12 (13)**	**255**		**50**
17	13 (14)	380		49
18	14 (15)	570		50
19	15 (16)	855		50
20	16 (17)	1300		52
21	17 (18)	2000		54

Boldface items signify the minimum tolerated dose required at initial escalation and dose build-up.

TABLE E4. *P* values for skin tests to other food and environmental allergens (compared with baseline)

	Soy	Cashew	Hazelnut	Walnut	Cat	Mite	Oak	Ragweed	Timothy
SLIT									
T4	<.001	.2	.1	.08	<.001	.2	.09	.04	.3
T5	.006	<.001	.1	.001	.014	<.001	.2	<.001	.4
T6	.4	.001	.5	.2	.7	<.001	.9	<.001	.5
OIT									
T4	—	.5	.8	—	.7	.003	.4	.3	.4
T5	—	.5	.9	—	.7	<.001	.7	.5	.003
T6	—	.2	.2	—	.8	.4	.9	<.001	.7

Note: There were insufficient numbers of subjects to perform analyses for soy or walnut.