HHS Public Access

Author manuscript

J Allergy Clin Immunol. Author manuscript; available in PMC 2016 May 01.

Published in final edited form as:

J Allergy Clin Immunol. 2015 May ; 135(5): 1275–1282.e6. doi:10.1016/j.jaci.2014.11.005.

A Randomized, Double-Blind, Placebo-Controlled Pilot Study of Sublingual versus Oral Immunotherapy for the Treatment of Peanut Allergy

Satya D. Narisety[1], **Pamela A. Frischmeyer-Guerrerio**[2,*], **Corinne A. Keet**[2], **Mark Gorelik**[2], **John Schroeder**[3], **Robert G. Hamilton**[3], and **Robert A. Wood**[2]

[1]Department of Pediatrics, Division of Allergy, Immunology and Infectious Diseases, New Jersey Medical School, Rutgers University, Newark, NJ

[2]Department of Pediatrics, Division of Allergy and Immunology, Johns Hopkins University School of Medicine, Baltimore, MD

[3]Department of Medicine, Division of Allergy and Immunology, Johns Hopkins University School of Medicine, Baltimore, MD

Abstract

Background—Although promising results have emerged regarding oral and sublingual immunotherapy (OIT and SLIT) for the treatment of peanut allergy, direct comparisons of these approaches are limited.

Objective—This study was conducted to compare the safety, efficacy, and mechanistic correlates of peanut oral and sublingual immunotherapy.

Methods—In this double-blind study, children with peanut allergy were randomized to receive active SLIT/placebo OIT or active OIT/placebo SLIT. Doses were escalated to 3.7mg/day (SLIT) or 2000mg/day (OIT), and subjects were re-challenged 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 month were taken off treatment for 4 weeks and re-challenged.

Results—Twenty-one subjects, age 7–13 years, were randomized. Five discontinued therapy during the blinded phase. Of the remaining 16, all had a >10-fold increase in challenge threshold after 12 months. The increased threshold was significantly greater in the active OIT group (141-fold versus 22-fold, P=0.01). Significant within group changes in skin tests and peanut-specific IgE and IgG4 were found with overall greater effects with OIT. Adverse reactions were generally

Contact: Robert A. Wood, MD, CMSC 1102, The Johns Hopkins Hospital, 600 N. Wolfe Street, Baltimore, MD 21287-3923, Phone: 410-955-5883, Fax: 410-955-0229, rwood@jhmi.edu.

*Pamela A. Frischmeyer-Guerrerio was employed by Johns Hopkins University at the time of this work. She is currently employed by the Division of Intramural Research, NIAID, NIH.

mild but more common with OIT (P<0.001), 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 peanut allergy, 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.

Keywords

peanut allergy; food allergy; immunotherapy; sublingual immunotherapy; oral immunotherapy

Introduction

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 rising.[1–6] Treatment for peanut allergy 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 and/or tree nut allergies accounting for the vast majority of fatal food-induced anaphylaxis.[9] Further, only about 20% of children outgrow their peanut allergy.[10]

In recent years, promising studies have emerged regarding oral[11–15] and sublingual immunotherapy[16,17] (OIT and SLIT) for the treatment of peanut allergy. 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, while OIT may be more effective, it also carries a higher risk of adverse reactions, presumably due to the higher doses used compared to SLIT. However, to date there have been no prospective, controlled studies comparing the two 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 peanut allergy. Additionally, extensive laboratory analyses were performed to better understand the immunological mechanisms underlying these treatments and their relationship to clinical outcomes. These mechanistic studies are provided in complete detail in the accompanying manuscript 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, 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 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 6–21 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 FDA under an investigational new drug application. Inclusion criteria included a physician diagnosis of PA, a positive peanut skin prick test (SPT, wheal 3mm ≥negative control), peanut-specific IgE ≥0.35 kUa/L (ImmunoCAP FEIA, Thermo-Fisher, Waltham, MA), and a convincing reaction to a cumulative dose of ≤1,000 mg of peanut protein in the baseline OFC (Supplemental Table 1B). Major exclusion criteria included a history of severe anaphylaxis to peanut with hypoxia, hypotension or neurological compromise, reaction to placebo during the qualifying OFC, poorly controlled atopic dermatitis, poorly controlled asthma, severe persistent asthma (requiring >500 mcg of fluticasone, or its equivalent, daily), and/or a diagnosis of eosinophilic esophagitis.

Study Protocol

Study Product—Treatments included peanut extract delivered by sublingual administration and peanut powder delivered by 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, 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 a history, physical exam, skin testing, phlebotomy, and an OFC with up to 1,000 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 (Figure 1 and Supplementary Tables 2 and 3). Initial treatment doses were 0.000165μg of peanut protein for SLIT and 0.1mg for OIT, which were escalated on the first treatment day to 0.066μg and 6mg, respectively. Over the next 16 weeks, subjects took daily home doses of SLIT followed by OIT and returned every 1–2 weeks for observed dose increases, with goal maintenance doses of 3.7 mg/day (SLIT) and 2000 mg/day (OIT) of peanut protein. This dose was then taken daily for 12 months, with 10 gram peanut protein OFC's conducted after 6 and 12 months of maintenance (Supplemental Table 1B), 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 re-challenged. 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 5–10 grams before reacting continued their prior treatment (SLIT or OIT) for 6 additional months, while those who reacted at <5 grams continued their current treatment and had either active SLIT or OIT added. SLIT was added at the full 3.7 mg dose while the 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 gram OFC and those who tolerated the OFC were taken off therapy for 4 weeks and re-challenged.

Study Procedures—The baseline OFC consisted of a cumulative dose of one gram of peanut protein using oat flour as placebo. Subsequent challenges utilized a cumulative dose of 10 grams. OFCs were double-blind through the blinded phase of the protocol and then performed as open challenges. OFCs were considered positive with clear objective signs (e.g. diffuse urticaria, wheezing) or convincing subjective symptoms (e.g. severe, persistent abdominal pain).

Skin prick testing (SPT) was performed at baseline and just prior to each OFC using peanut extract (Greer Laboratories, Lenoir, NC), serial ten-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), using the Greer Pick device.

Laboratory studies included peanut-specific IgE and IgG_4 levels which were measured prior to each OFC (ImmunoCAP). In addition, extensive mechanistic studies, described in detail in the accompanying manuscript[18] were performed prior to each OFC, including spontaneous and stimulated basophil activity, allergen-induced cytokine expression in expression in dendritic cell (DC)-T cell co-cultures by multiplexing technology, and peanut-induced expression of MHC II and costimulatory molecules on DCs by flow cytometry.

Statistical Analysis

Differences between SLIT and OIT for the primary outcome, a 10-fold increase in OFC threshold, were analyzed by Fisher's exact test, and quantitative differences in fold-increase OFC threshold between the groups was evaluated by the Mann-Whitney-U test. Changes with treatment in OFC threshold, IgE and IgG4, and skin tests were analyzed by linear regression models using generalized estimating equations to account for repeated measures over time with robust standard errors. Analysis of skin test responses to non-peanut allergens included only those subjects with positive tests at baseline. Specific IgE and IgG4 values were log transformed for analysis. Outcomes were analyzed by both by 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 chisquared tests or Fisher's exact tests, as appropriate, including percentage of doses with symptoms during treatment.

Results

Study participants

Twenty-one subjects, 7–13 years, were randomized, including 10 in the active SLIT/placebo OIT group and 11 in the active OIT/placebo SLIT group (Figure 1). There were no significant differences between the two groups with regard to age, peanut-specific IgE (median 163 versus 169 kU/l), peanut-specific IgG4, peanut SPT or endpoint SPT results, or baseline OFC results (median cumulative dose 21mg for both groups) (Table 1).

Dose escalation and build up

On initial dose escalation, all 10 subjects in the active SLIT group escalated to the maximum dose of .066μg, while only 5/11 in the active OIT group reached the maximum of 6mg. Of the remaining 6, one reached 1.5mg, two reached 2.5mg, two reached 3.5mg, and one reached 5mg. Twenty subjects completed the 16 week dose build up and continued to maintenance dosing. One subject from the OIT group withdrew from the study after dose escalation due to a diagnosis of eosinophilic esophagitis, which was determined to be unrelated to the study given that it occurred after just one day of dosing and did not resolve after 12 weeks of peanut avoidance.

Maintenance therapy

Sixteen subjects (9 active SLIT, 7 active OIT) were able to complete therapy and undergo both OFCs after 6 months and 12 months of maintenance. One subject on active SLIT discontinued due to persistent gastrointestinal symptoms while three on active OIT discontinued, one with persistent gastrointestinal symptoms, one after a systemic reaction with home dosing, and one due to noncompliance.

OFC results

All 16 subjects who completed OFCs after maintenance had increases in their cumulative challenge threshold compared to baseline (Figure 2). Seven of 10 of the original active SLIT group and 7/11 on active OIT achieved the primary endpoint of a 10-fold increase compared to baseline ($p=0.76$ between groups). In the 9 SLIT subjects, the median cumulative dose increased from a baseline of 21mg (range 1–146mg) to 496mg (range 146–3246mg) after 6 ($p=0.01$) and 496mg (range 71–3246mg) after 12 months ($p=0.02$). In the 7 OIT subjects completing maintenance, threshold doses increased from 21 mg (range 6–146mg) to 7246mg (range 146–10,000mg) after 6 ($p<0.001$) and 7246mg (range 146–10,000mg) after 12 months ($p<0.001$).

Between groups, the increase in 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) were significantly greater with OIT ($p=0.009$ and $p=0.01$). 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 added, of whom 2 were unable to complete the OIT build-up due to persistent gastrointestinal symptoms. The other 7 achieved active OIT maintenance and were re-challenged after 6 months with a median OFC dose of 10,000mg (range 6000–10,000 mg, $p<0.0001$ compared to OFC after 12 months of SLIT alone). From the original active OIT group, one subject passed his OFC at the end of the blinded phase and was taken off treatment for 4 weeks and re-challenged, 3 extended their OIT for 6 months (all tolerating 10,000mg in their end of treatment OFC), and the other 3 continued OIT and added active SLIT for 6 months before being re-challenged (median OFC cumulative dose 10,000mg, range 996–10,000mg, $p=0.08$ compared to OFC after 12 months of OIT alone).

Transient versus Sustained Desensitization

As noted, one subject from the active OIT group passed his OFC upon the 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 from the active SLIT group who completed the 6 months of add-on OIT passed their end of treatment OFC and, upon re-challenge, their median cumulative dose was 7246 mg (range 496–10,000 mg) with only one passing the challenge. In the other four, two reacted at 496mg, one reacted at 7,246mg, and one reacted at 8,000mg. Of the 6 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, 1/10 originally assigned to SLIT and 3/11 assigned to OIT had sustained unresponsiveness (p=0.59).

Skin Test Results

SPT's using full strength peanut extract decreased in both groups through the blinded phase [SLIT: baseline median wheal 9.3mm, 5.5mm after 6 (p=0.10) and 12 months (p=0.047) of maintenance; OIT: baseline median 12 mm, 4.5mm after 6 months (P<0.001), 0mm after 12 months (P<0.001)]. With regard to endpoint SPT, the average wheal size for the 5 concentrations of peanut decreased significantly in both groups (Figure 3). For the SLIT group, the median average wheal size decreased from 4.75mm at baseline to 1.6mm at 6 months (p=0.004) and 1.5mm at 12 months (p<0.001). For the OIT group, the median average wheal size decreased from 5.8mm at baseline to 1mm after 6 months and 0mm after 12 months (p<0.001 for both).

Comparison of the SLIT and OIT groups revealed similar changes in SPT results over time, with the exception of greater changes in the OIT group at T4 for both the full strength and endpoint SPT (P=0.01 and 0.03, respectively) and for full strength SPT at T5 (P=0.03). 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 non-peanut food antigens to assess for possible non-specific treatment effects (Supplemental Figure 1 and Supplemental Table 3). At baseline, positive SPTs 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 in 9. Significant changes in SPT wheal size were seen for several allergens, especially in the OIT group. While no consistent pattern was evident, with apparent effects on both food and environmental allergens, many of these changes occurred early in treatment and had disappeared later in the study.

Serologic outcomes

Peanut-specific IgE increased initially and subsequently decreased over time for both groups (Figure 4). For the SLIT group, the median increased from 163 kUa/L (range 37.5–746) at baseline to 369 (range 47.4–1960) by the end of dose build up (p<0.001), remained higher after 6 months of maintenance (median 387 kUa/L, p=0.04) and was not different from baseline after 12 months of maintenance (median 273, p=0.91). In the OIT group, the

median increased from 169 kUa/L (range 35.1–716) at baseline to 392 kUa/L (range 84–1069) by the end of dose build up (p=0.001), after which medians fell to 68 and 53 kUa/L after 6 and 12 months (p=0.19 and <0.001 compared to baseline, respectively). Between groups, decreases in peanut IgE were greater in the OIT group at 6 and 12 months (p=0.07, p=0.007). Further decreases in peanut IgE occurred in both groups during unblinded treatment.

Peanut-specific IgG4 increased in both groups over the study (Figure 5). For the SLIT group, median levels increased from 0.9 mgA/L at baseline to 2.5 at the end of dose build up (p=0.001), 7.9 after 6 months (p<0.001), and 8.5 after 12 months (p<0.001). For the OIT group, median levels increased from 1.3 mgA/L at baseline to 11.3 at the end of dose build up (p<0.001), 83.4 after 6 months (p<0.001), and 76 after 12 months (p<0.001). Between groups, there was overall a greater change from baseline in the OIT group [end of dose build up (p=0.003), after 6 and 12 months (p<0.001)]. In the unblinded phase, the addition of OIT to SLIT resulted in a further increase in peanut IgG4 (p=0.003).

Correlation of laboratory and clinical outcomes

Subjects who had sustained unresponsiveness had lower peanut IgE at baseline (median 79 versus 257, p=0.02) and greater decreases in IgE at T4 (p=0.02). There were no significant relationships between OFC outcomes and baseline SPT, endpoint SPT, peanut IgG4, or changes in these measures over time. Detailed mechanistic assessments and their relationship to the clinical outcomes are provided in the accompanying manuscript.

Adverse Reactions with Dosing

In the blinded phase, a total of 4,578 doses were taken by the SLIT group and 4,049 by the OIT group (Table 2). Overall, the proportion of doses with adverse reactions was significantly higher in the OIT group (43% versus 9% of doses, p<0.001). Most reactions were mild, although a small percentage were moderate in severity (3.4% versus 1.3%, p<0.001). With regard to specific symptoms, all were more common in the subjects on OIT (e.g. oral/pharyngeal 24.2% versus 3.9%, respiratory 6.9% versus 0.6%, gastrointestinal 9.0% versus 3.2%; p<0.001 for all). When adverse reactions were assessed per subject, 9/10 SLIT subjects and 10/10 OIT subjects had symptoms with dosing (p=1.0), with medians of 29 and 149 doses with symptoms (p=0.008).

Antihistamines were used to treat symptoms in 40.9% of OIT doses versus 23.1% of SLIT doses (p<0.001). This significant difference was present through all three phases of the blinded study. β_2-gonists were also used for a significantly higher percentage of doses in the OIT group (1.9% versus 0.3%, p<0.001). Five doses of epinephrine were required to treat systemic reactions in 4 subjects in the active OIT group, one during dose build up and four during maintenance.

In the unblinded phase, symptoms were experienced at a rate of 5.1% of 2,599 total doses taken by active SLIT/active OIT add on subjects, 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 3). Antihistamines were used for 1.4%, 22.3% and 0.4% of doses, while β_2 agonists were used in 0.2%, 7.4% and 0.4% of doses. Injectable epinephrine was required by one 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 oral and sublingual immunotherapy for peanut or other food allergy 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 CoFAR[17] (SLIT) and Jones and Burks (OIT).[12–14] Although the study is limited by a small sample size and a high drop-out 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 threshold compared to baseline. However, the degree of desensitization was far greater in those on OIT compared to SLIT, with subjects tolerating an average of approximately 24 peanuts compared to 1–2 peanuts. This is similar to results of the CoFAR peanut SLIT study in which most subjects increased their OFC threshold at least 10-fold, but none reached the maximum OFC dose of 5 grams 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 gram challenge, and even had the opportunity to be assessed for sustained unresponsiveness.

However, while the potential benefit of OIT appears far greater than that afforded by SLIT, the differences in safety between the two 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-gonists, or injectable epinephrine. Further, OIT was associated with a far greater number of treatment withdrawals due to intolerable symptoms. These results are overall similar to our recent open label study comparing SLIT to 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. Based on this design, all subjects on active SLIT had active OIT added for an additional 6 months of maintenance. Although the group is too small to draw any firm conclusions, three important themes emerge. First, adding OIT to SLIT led to significant increases in challenge threshold; second, pre-treatment with SLIT appeared to provide substantial protection against adverse reactions; and third, while the protection from adverse reactions appeared quite dramatic overall, 2/9 still dropped out during OIT build-up due to 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 since only one subject (on OIT) was eligible for assessment of sustained unresponsiveness. This is not surprising since SLIT appears unlikely to induce that

degree of desensitization, and even with OIT, this short course of treatment may 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 gram 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 tests, as well as peanut-specific IgE and IgG4. Although OIT did induce somewhat greater changes in each of these parameters, and we did find that a lower baseline peanut IgE 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 non-specific effects of peanut immunotherapy, using sequential skin testing to other food and environmental allergens. While these data are limited by the fact that not all subjects were sensitized to these allergens, as well as by the high drop-out 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. Further, 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 on OIT who were sensitized to cat at baseline had no skin test reactivity after 6 months, while all had returned to baseline by the end of treatment. The reasons for these findings are not clear but are especially interesting given the results in the accompanying mechanistic paper, demonstrating that the immunologic effects of immunotherapy may 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 drop-outs due to adverse reactions. While pre-treatment 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, while 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 and/or modified allergens.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding:

Supported by grants from:

Grant Number UL1 TR 001079 from the National Center for Advancing Translational Sciences (NCATS) a component of the National Institutes of Health (NIH), and NIH Roadmap for Medical Research.

The Research Training in Pediatric Allergy and Immunology, Grant # 5T32AI007007

NIH Grant K23 AI091869

The Winkelstein Fellowship Fund

ARTrust Faculty Development Award

Johns Hopkins University Clinician Scientist Award

National Institutes of Health (NIH) R21 Research Award (AI079853; J.T.S.)

National Institute of Health Asthma and Allergic Diseases Cooperative Research Centers grant, (U19AI070345-01; J.T.S.)

Food Allergy Research and Education (FARE) grant (R.A.W)

P. A. F.-G. is supported by the Division of Intramural Research, National Institute of Allergy and Infectious Diseases, NIH

Abbreviations

DC	Dendritic cell
FDA	Food and Drug Administration
OFC	Oral food challenge
OIT	Oral immunotherapy
PA	Peanut allergy
SLIT	Sublingual immunotherapy
SPT	Skin prick test

References

1. Sicherer SH. Epidemiology of food allergy. J Allergy Clin Immunol. 2011; 127(3):594–602. [PubMed: 21236480]
2. Sicherer SH, Munoz-Furlong A, Godbold JH, et al. US prevalence self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol. 2010; 125(6):1322–1326. [PubMed: 20462634]
3. Liu AH, Jaramillo R, Sicherer SH, et al. National prevalence and risk factors for food allergy and relationship to asthma: results from the National Health and Nutrition Examination Survey 2005–2006. J Allergy Clin Immunol. 2010; 126:798–806. [PubMed: 20920770]
4. Jackson KD, Howie LD, Akinbami LJ. Trends in allergic conditions among children: United States 1997–2011. NCHS Data Brief. 2013; (121):1–8. [PubMed: 23742874]
5. Sicherer SH, Munoz-Furlong A, Godbold JH, Sampson, et al. US prevalence of self-reported peanut, tree nut, and sesame allergy: 11-year follow-up. J Allergy Clin Immunol. 2010; 125:1322–6. [PubMed: 20462634]

6. Rinaldi M, Harnack L, Oberg C, Schreiner P, St Sauver J, Travis LL. Peanut allergy diagnoses among children residing in Olmsted County, Minnesota. J Allergy Clin Immunol. 2012; 130:945–50. [PubMed: 22944484]
7. Neuman-Sunshine DL, Eckman JA, Keet CA, et al. The natural history of persistent peanut allergy. Ann Allergy Asthma Immunol. 2012; 108(5):326–331.e3. [PubMed: 22541403]
8. Sicherer SH, Burks AW, Sampson HA. Clinical features of acute allergic reactions to peanut and tree nuts in children. Pediatrics. 1998; 102(1):e6. [PubMed: 9651458]
9. Sampson HA, Munoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. J Allergy Clin Immunol. 2005; 115(3):584–591. [PubMed: 15753908]
10. Skolnick HS, Conover-Walker MK, Koerner CB, et al. The natural history of peanut allergy. J Allergy Clin Immunol. 2001; 107(2):367–374. [PubMed: 11174206]
11. Clark AT, Islam S, King Y, et al. Successful oral tolerance induction in severe peanut allergy. Allergy. 2009; 64(8):1218–1220. [PubMed: 19226304]
12. Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009; 124(2):292–300. [PubMed: 19577283]
13. Hofmann AM, Scurlock AM, Jones SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol. 2009; 124(2):286–291. 291 e281–286. [PubMed: 19477496]
14. Varshney P, Steele PH, Vickery BP, et al. Adverse reactions during peanut oral immunotherapy home dosing. J Allergy Clin Immunol. 2009; 124(6):1351–1352. [PubMed: 19913285]
15. Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol. 2010; 126(1):83–91. [PubMed: 20542324]
16. Kim EH, Bird JA, Kulis M, et al. Sublingual immunotherapy for peanut allergy: Clinical and immunological evidence of desensitization. J Allergy Clin Immunol. 2011; 127(3):640–646.e1. [PubMed: 21281959]
17. DFleischer DM, Burks AW, Vickery BP, et al. Sublingual immunotherapy for peanut allergy: A randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013; 131(1):119–127.e7. [PubMed: 23265698]
18. Gorelik M, Narisety SD, Guerrerio AL, Chichester K, Keet CA, Bieneman AP, et al. Immunologic Suppression To Peanut During Immunotherapy May Be Transient. (submitted).
19. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012; 129(2):448–455. 455.e1–5. [PubMed: 22130425]
20. 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; 132:476–8. [PubMed: 23534975]
21. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral Immunotherapy for Treatment of Egg Allergy in Children. NEJM. 2012; 367:233–43. [PubMed: 22808958]
22. 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(2):468–75. [PubMed: 24361082]

Clinical Implications

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

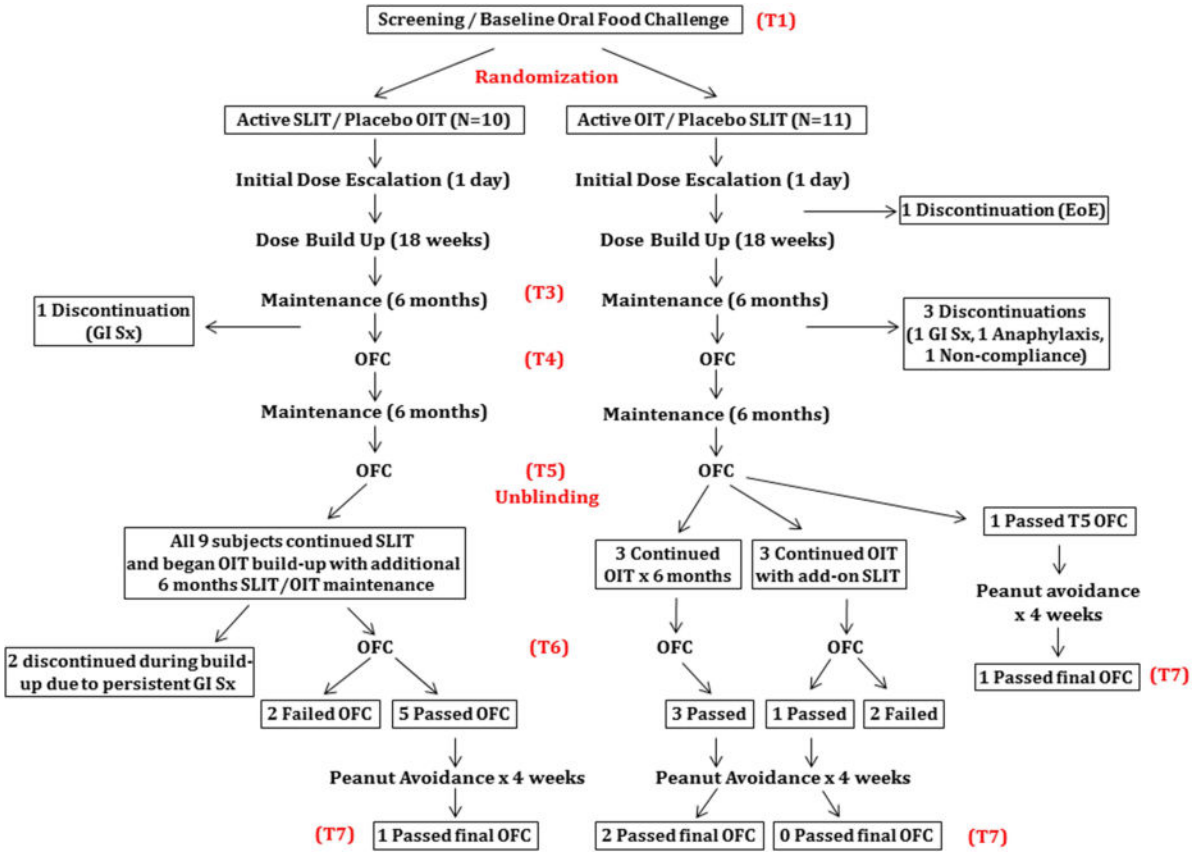


Figure 1.

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

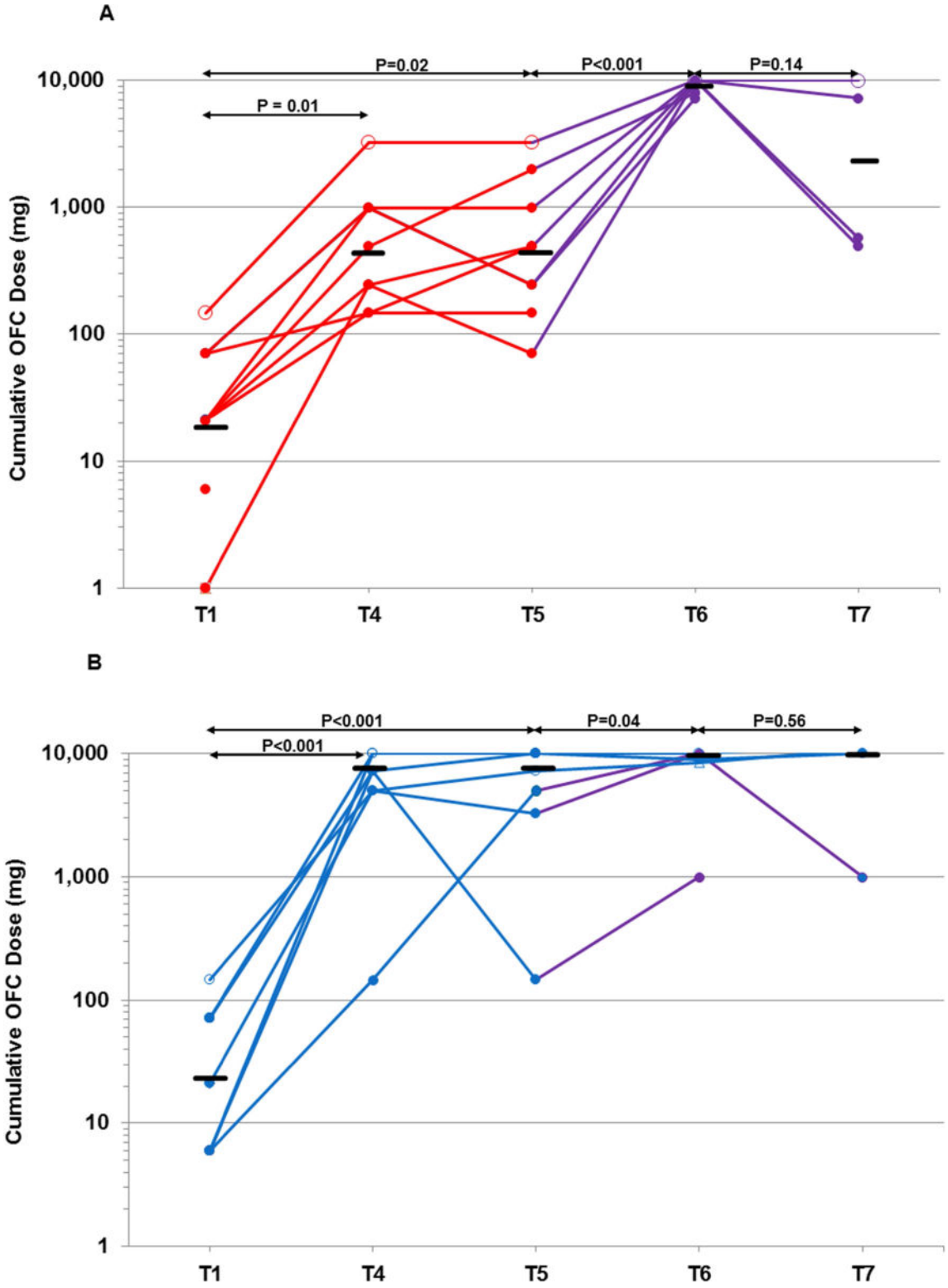


Figure 2.

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 threshold with OIT compared to SLIT (p=0.008 and p=0.01 after 6 and 12 months of maintenance).

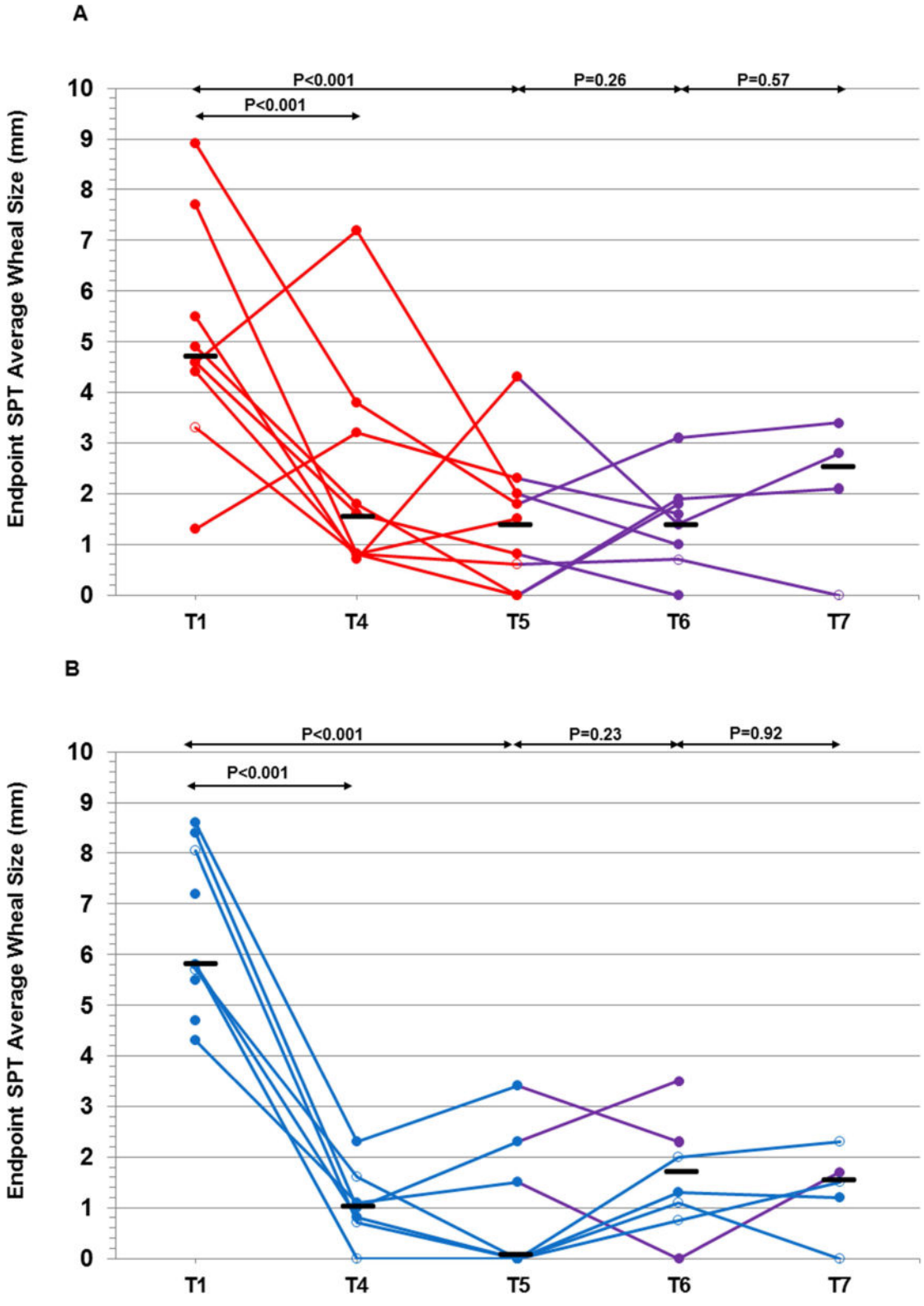


Figure 3.

Change in endpoint 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=0.03).

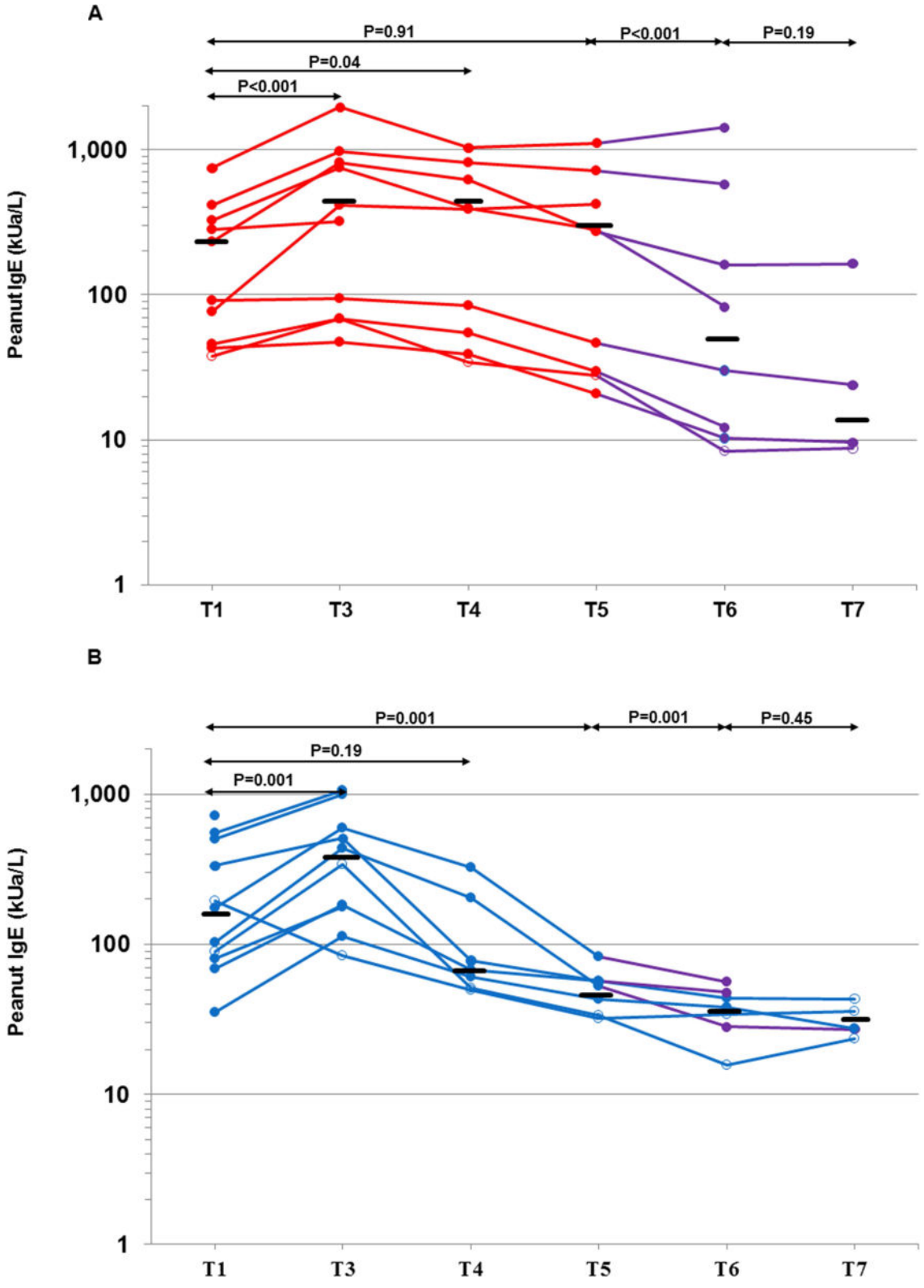
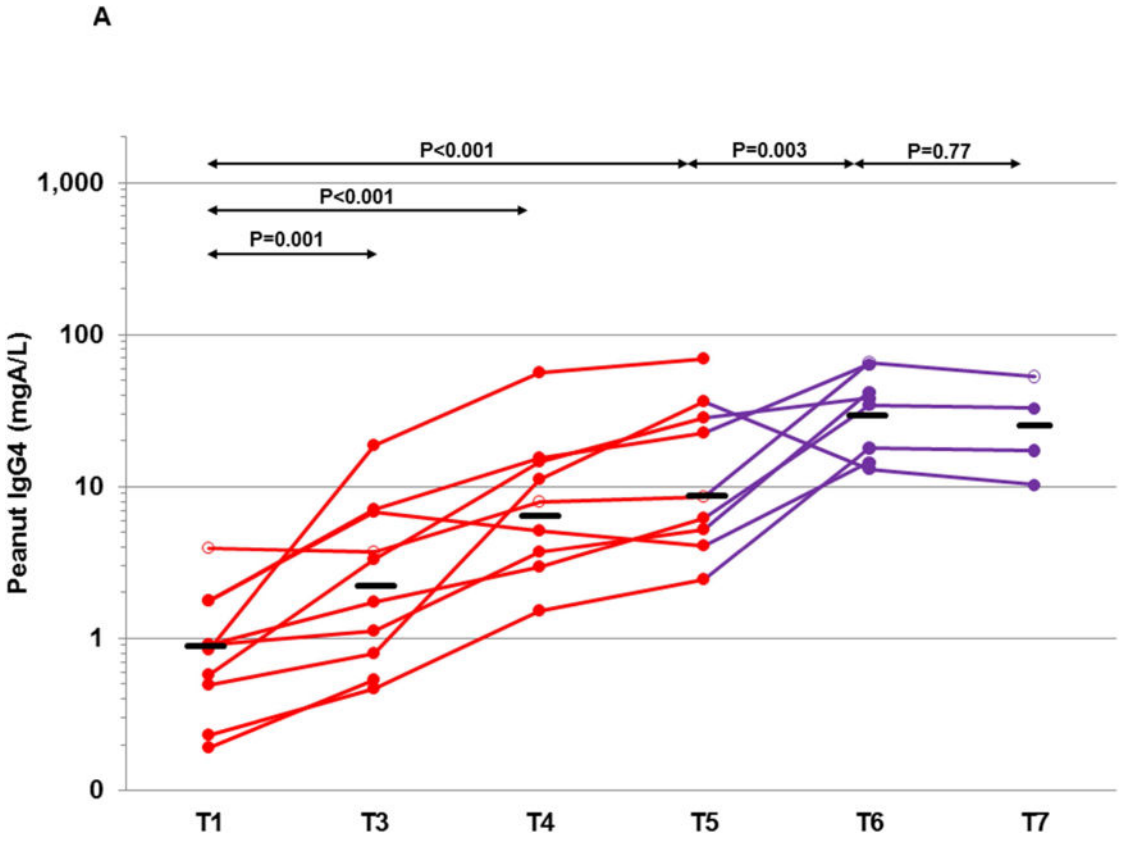


Figure 4.

Change in peanut-specific IgE 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 was greater in the OIT group, and this difference widened by 12 months ($p=0.07$, $p=0.007$, respectively).



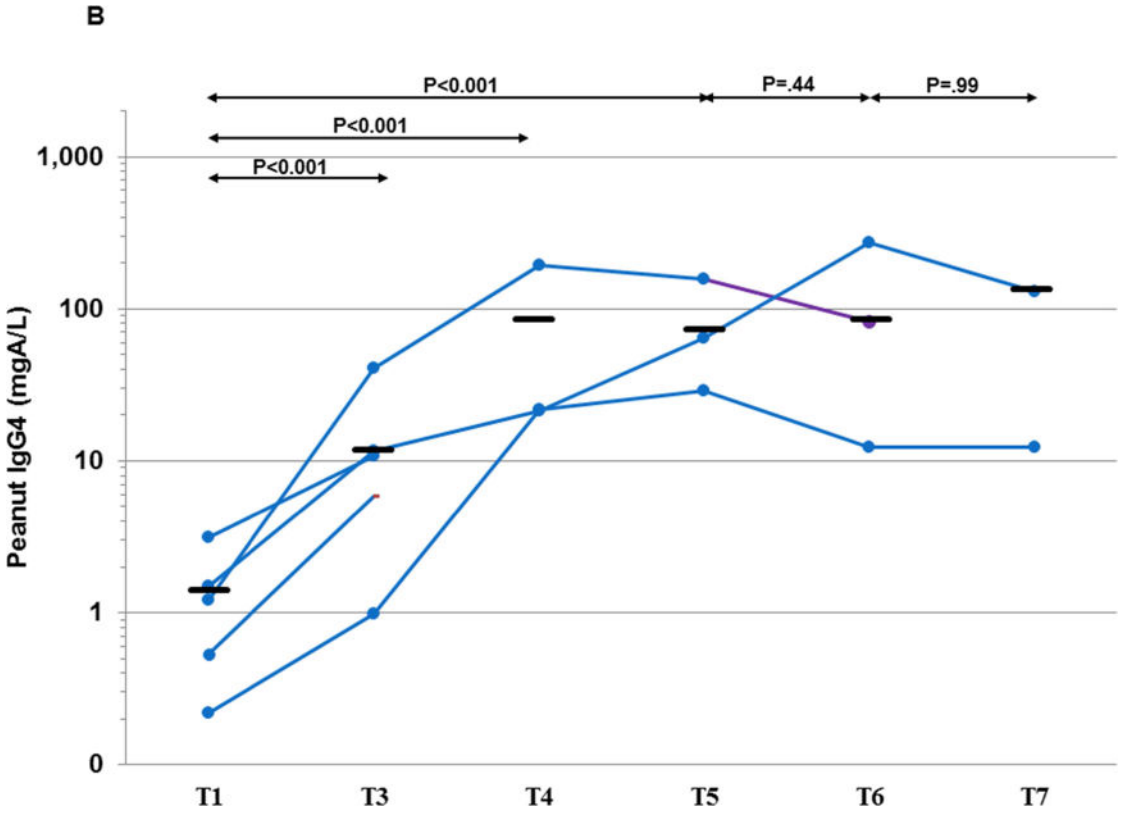


Figure 5.

Change in peanut-specific IgG4 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 IgG4 values over time in the OIT group compared to the SLIT group at all time points [end of dose build up ($p=0.003$), after 6 and 12 months of maintenance ($p<0.001$)].

Table 1

Subject Demographics

	Active OIT/Placebo SLIT	Active SLIT/Placebo OIT
Total subjects (n)	11	10
Age (yrs), median (range)	11.1 (9.7–13)	11.1 (7.2–12.4)
Gender (male)	7 (64%)	4 (40%)
Prior history of peanut anaphylaxis (# subjects)	6	1
Other food allergies (# subjects)	10	10
Atopic dermatitis (# subjects)	6	6
Asthma (# subjects)	9	4
Allergic rhinitis (# subjects)	10	9
Peanut IgE (kUa/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 endpoint 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

Table 2

Blinded Phase: Summary of adverse events

Treatment Group	Total doses (n)	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

Table 3

Unblinded Phase: Summary of adverse events

Treatment Group	Total doses (n)	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