

Efficacy of allergen-specific immunotherapy for peanut allergy: A meta-analysis of randomized controlled trials

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ABSTRACT

Peanut allergy is one of the most common food allergies. Allergen-specific oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) for peanut allergy aim to induce desensitization and then tolerance to peanuts. However, there is still considerable uncertainty about the safety of these two approaches and if the risk is justified by the benefit of the therapy. We performed a systematic review and meta-analysis to assess the efficacy and safety of OIT and SLIT in patients with peanut allergy. We performed searches of the MEDLINE, CINAHL, EMBASE, ISI Web of Science, and Cochrane databases (through March 18, 2013) for randomized controlled trials (RCTs) that compared OIT or SLIT with a placebo in patients with peanut allergy. The study selection and data extraction were independently performed by two reviewers. The primary outcome was the proportion of patients whose condition improved. We also analyzed immunologic changes and adverse events. A meta-analysis was performed using a random effects model. Three RCTs that comprised a total of 86 subjects were analyzed. OIT or SLIT had a significantly positive effect on peanut allergy (odds ratio [OR], 38.44; 95% confidential interval [CI], 6.01–245.81). Several immunologic changes associated with the induction of tolerance were improvements. There is no difference between the OIT or SLIT group and placebo group in the number of patients who required epinephrine during the study (OR, 0.51; 95% CI, 0.03–10.20). This study showed a statistically significant benefit of peanut immunotherapy in patients with peanut allergy. However, these findings are based on an analysis of a small number of RCTs. Additional larger, well-designed and double-blind RCTs are needed.

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Peanut allergy is a life-threatening, IgE-mediated allergic disease. This allergy is one of the most common food allergies and is estimated to affect >1% of school-aged children in developed countries.^{1–3} Many of these patients develop severe symptoms on exposure, and only minute quantities can induce an anaphylactic reaction.^{4–6} All peanut-allergic individuals are counseled about strict dietary avoidance and given self-injectable epinephrine.

Clinical peanut allergy is typically lifelong.^{7–9} Therapeutic interventions that provide permanent protection against unintentional peanut ingestion are therefore needed. The defining immunopathological feature of peanut allergy is the presence of circulating peanut protein-specific IgE antibodies in the susceptible individual. Therefore, any approach that reduces the levels of IgE has the potential to reduce allergic sensitivity. Allergen-specific immunotherapy for peanut allergy is one of the most studied research options. To date, 11

peanut allergens (Ara h1–11) have been identified,¹⁰ and the three major allergenic proteins are Ara h1, Ara h2, and Ara h3.^{11–13} The identification of these antigens has been very helpful for the development of allergen-specific immunotherapy.

Twenty years ago, small placebo-controlled trials of subcutaneous immunotherapy for peanut allergy were undertaken. Although the results were promising in certain respects, the frequency of adverse events was high.^{14,15} Oral immunotherapy (OIT) and sublingual immunotherapy (SLIT) are now being investigated as two effective, safer modes of immunotherapy in people with peanut allergy.^{16–19} However, at present, there is still considerable uncertainty about the safety of these two approaches and if the risk is justified by the benefit of the therapy.^{17–22} Whether immunotherapy for peanut allergy is ready for clinical practice is still controversial. Therefore, we performed a meta-analysis of data from published randomized controlled trials (RCTs).

METHODS

This study was conducted in accordance with the Cochrane Handbook for Systematic Reviews.²³

Search Methods for Identification of Studies

We conducted systematic searches regardless of language, geographical area, or publication status. The

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date of the last search of all databases was March 18, 2013.

Electronic Searches

Using the terms “peanut hypersensitivity,” “peanut allergy,” “immunotherapy,” “immune therapy,” and “desensitization” we searched the following databases: MEDLINE, CINAHL, EMBASE, ISI Web of Science, and the Cochrane Library. The search was limited to human studies.

Searching Other Resources. To identify unpublished and ongoing work, we searched relevant Internet-based databases: Current Controlled Trials, ClinicalTrials.gov, and Australian New Zealand Clinical Trials Registry. We also searched the references of all studies identified by the aforementioned methods.

Criteria for Considering Studies for This Review

We were interested in RCTs investigating peanut immunotherapy (OIT or SLIT) compared with either a placebo group or a peanut-avoidance control group and performed in children or adults with confirmed peanut allergy. The study did not include any duplicate publications, substudies, or studies in which the control group received anything beyond conventional treatment. To avoid the double counting of patients included in more than one article by the same authors or research groups, patient recruitment periods were evaluated, and if necessary, authors were contacted for clarification.

Assessment of Risk of Bias in Included Studies

Two researchers (J.S. and D.L.) independently assessed the risk of bias in each trial using the Cochrane Collaboration’s Risk of Bias tool. We assessed the risk of bias during random sequence generation, allocation concealment, the blinding of participants and personnel, the blinding of outcome assessment, the analysis of incomplete outcome data, and selective reporting and in other areas. All of these judgments were categorized as “yes” (low risk of bias) or “unclear” or “no” (high risk of bias).²⁴

Primary Outcomes

We considered outcomes measured in any time period during or after treatment. We only included studies that assessed our primary outcomes of interest. One primary outcome of interest was the proportion of patients whose condition improved regardless of different evaluation methods. Treatment success was defined as tolerated peanut protein increased to a defined amount from the start of therapy. We also analyzed immunologic changes suggestive of the induction of tolerance, including decreased titrated skin-prick test

(SPT) size, decreased peanut-specific IgE levels, and increased peanut-specific IgG4 levels. Adverse events were also evaluated.

Data Collection and Analysis

Two reviewers (X.H. and W.Y.) independently reviewed the titles and abstracts retrieved during the search process and selected all studies that potentially satisfied our inclusion criteria. Both reviewers then independently assessed the full texts of these potentially eligible studies against the inclusion criteria. If no agreement was reached, a third reviewer (J.S.) arbitrated. We collected the details of included studies using a form designed for this purpose. The following data were, where available, independently extracted from the included studies: study type and methodology, the number and description of subjects, a description of the intervention, outcomes, timing, measurement methods, and adverse events.

For dichotomous data, we calculated individual and pooled statistics as an odds ratio (OR) with 95% confidence intervals (CIs). We conducted a meta-analysis using a random effects model. Clinical or statistical heterogeneity among studies was analyzed using the I^2 statistic and significant heterogeneity assumed if I^2 is $>40\%$ (i.e., $>40\%$ of the variability in outcome between trials could not be explained by sampling variation). *Post hoc* sensitivity analysis was conducted to examine whether the overall finding was robust to one or two outlying studies. In the sensitivity analysis, sequential meta-analyses, in which each study was excluded, were repeated. The analysis was performed using Review Manager, Version 5.2 (Cochrane IMS, Copenhagen, Denmark).

RESULTS

Search Results

After removing duplicates, our searches initially identified a total of 401 records, 75 of which we selected for more detailed interrogation. In total, 72 studies were excluded because they were case reports ($n = 2$), review articles ($n = 55$), or not RCTs ($n = 9$); did not test SLIT or OIT ($n = 3$); or did not report our primary outcomes ($n = 3$). After exclusions, three RCTs^{25–27} with a total of 86 patients were available for analysis (Fig. 1).

Included Studies

All three included studies^{25–27} were double-blind, placebo-controlled RCTs and were conducted in the United States (Table 1). In the three studies, peanut allergy was diagnosed according to the clinical history of reaction to peanuts and the peanut-specific IgE level. In addition, in one study,²⁶ the diagnosis was confirmed by a positive SPT response, and in another

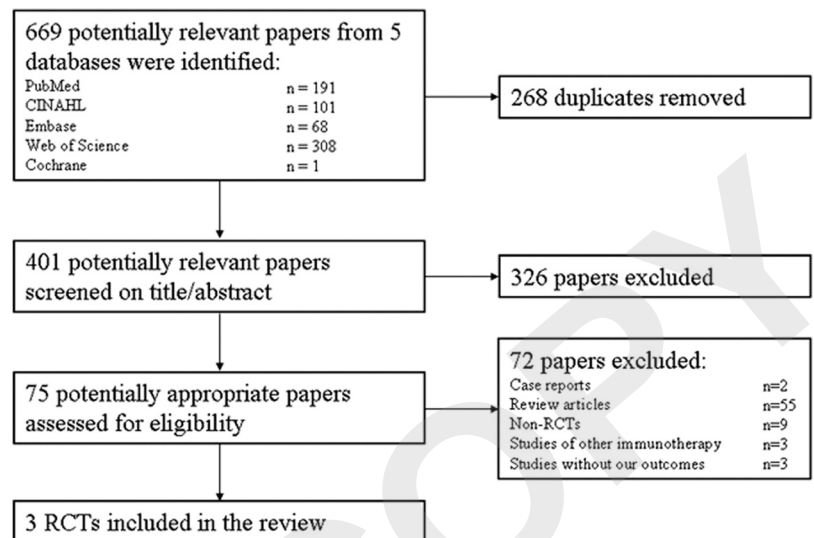


Figure 1. Flow diagram for selecting studies.

study,²⁷ the diagnosis was confirmed by a positive peanut SPT response and a positive baseline double-blind, placebo-controlled food challenge (DBPCFC) with peanuts. Patients with a history of severe peanut anaphylaxis were excluded from all three studies.

One study²⁶ tested the effects of OIT, and two studies^{25,27} tested the effects of SLIT. In the OIT study,²⁶ the active treatment was peanut flour, compared with a placebo of oat flour. A DBPCFC was conducted at week 48. In the two SLIT studies,^{25,27} the active treatment was sublingual peanut drops, compared with a placebo. A DBPCFC was conducted at month 12 and weeks 44 and 68, respectively. Adverse events were recorded and peanut-specific IgE and IgG4 levels were measured in all three studies.

Risk of Bias in Included Studies

All of the included studies were described as randomized and provided specific details about the method of randomization. One study²⁶ provided specific details about the concealment of allocation. The blinding of study subjects and investigators was considered adequate in all studies. In the study by Kim *et al.*,²⁵ the laboratory staff was unblinded throughout the study. The results are summarized in the “risk-of-bias” graph (Fig. 2). Figure 3 presents a summary of each risk-of-bias item for each included study.

Effects of Interventions

A total of 50 patients were included in the treatment groups, and 36 patients were in the control groups. In each included study, there were no statistical differences in baseline characteristics between treatment group and placebo group, and treatment group safely ingested more peanut protein than placebo group after the completion of treatment. The proportion of patients who tolerated a defined amount of peanut protein by

oral challenge after the completion of treatment was evaluated. In the study by Kim *et al.*,²⁵ 11/11 patients in the treatment group passed a 1.71-g peanut protein challenge compared with 0/7 in the placebo group. In the study by Varshney *et al.*,²⁶ 16/19 patients in the treatment group tolerated a 5-g peanut protein challenge compared with 0/9 in the placebo group. In the study by Fleischer *et al.*,²⁷ 14/20 subjects receiving peanut SLIT were responders compared with 3/20 subjects receiving a placebo. A random effects model, pooling the results, showed that OIT and SLIT had a significantly positive effect on peanut allergy (for all three studies, OR, 38.44 and 95% CI, 6.01–245.81; Fig. 4). Sensitivity analysis (each study was sequentially excluded) revealed that the result was not dependent on any individual study (Table 2).

Immunologic Changes

We also analyzed immunologic changes (titrated SPT size, peanut-specific IgE, and IgG4 levels) in the study. However, the results of the three indicators were reported as medians, and there was a difference in the methods of reporting among the three studies, so these data could not be analyzed quantitatively.

In the study by Varshney *et al.*,²⁶ the titrated SPT size decreased from a median of 7 mm (range, 5.5–15 mm) at baseline to 1.75 mm (range, 0–10 mm) in the peanut OIT group at oral food challenge (OFC), and no significant change was noted in the placebo group. Median peanut-specific IgE levels increased nearly threefold (to 308 kU/L) by 2 months in peanut OIT subjects (baseline 104 kU/L). However, there is no significant difference from baseline to OFC. Peanut-specific IgG4 levels significantly increased from baseline to all time points during peanut OIT and did not change during placebo treatment.

Table 1 Characteristics of studies included in the review

Study	Study Design	Diagnosis Criteria	Participants	Intervention Type	Day 1 Protocol	Maintenance Protocol	Duration	Outcomes
Kim <i>et al.</i> ²⁵	RCT DB PC	Clinical history of reaction to peanuts and peanut-specific IgE level ≥ 7 kU/L	18 children (1–11 yr old)	SLIT	Single 0.25 μ g-dose administered	Slow desensitization to 2000- μ g target	12 mo	Effects of SLIT, immunological changes, and adverse events
Varshney <i>et al.</i> ²⁶	RCT DB PC	Clinical history of reaction to peanuts, peanut-specific IgE level >15 kU/L or >7 kU/L if significant reaction occurred within 6 mo of enrollment, and positive SPT ≥ 3 mm	28 children (28–126 mo old)	OIT	6 mg (not tolerating at least 1.5 mg were withdrawn)	Build to $4 \times g$ target	48 wk	Effects of OIT, immunological changes, and adverse events
Fleischer <i>et al.</i> ²⁷	RCT DB PC	Clinical history of reaction to peanuts, positive SPT >3 mm or peanut-specific IgE level ≥ 0.35 kU/L, and positive DBPCFC result for peanuts	40 children and adults (12.2–36.8 yr old)	SLIT	Started at 0.000165 μ g	First phase, build to 1386- μ g target; maximum to 3696 μ g	68 wk	Effects of SLIT, immunological changes, and adverse events

RCT = randomized controlled trial; DB = double blind; PC = placebo controlled; SLIT = sublingual immunotherapy; OIT = oral immunotherapy; DBPCFC = double-blind, placebo-controlled food challenge.

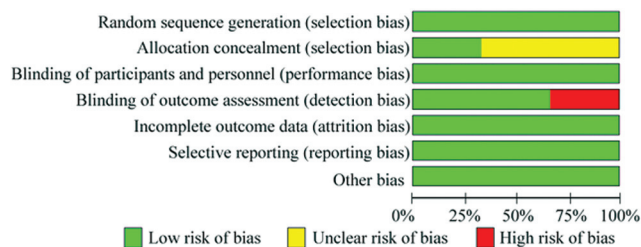


Figure 2. Risk-of-bias graph. Our judgment of each risk-of-bias item is presented as a percentage for all included studies.

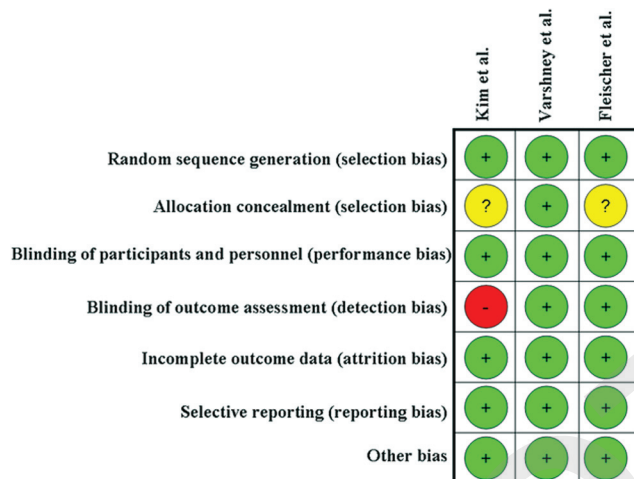


Figure 3. Risk-of-bias summary. Our judgment of each risk-of-bias item for each included study.

In the study by Kim *et al.*,²⁵ SPT size in the peanut SLIT group (4 mm; range, 0–11 mm) was significantly lower than in the placebo group (11.5 mm; range, 3.5–21 mm) after 12 months of treatment. Compared with those in the placebo group, peanut-specific IgE levels in the peanut SLIT group significantly decreased to a median level of 31.4 kU/L after 8 months of treatment, and after 12 months of treatment, peanut-specific IgG4 levels were significantly higher in the peanut SLIT group (1.12 mg/L; range, 0.1–22 mg/L).

In the study by Fleischer *et al.*,²⁷ peanut end point titration SPT was performed at baseline and week 68. There was no statistically significant difference between peanut SLIT responders and nonresponders in the baseline peanut SPT score or area-under-the-curve analysis for end point titration SPTs. Peanut-specific IgE and IgG4 levels significantly increased from baseline (20.1 kU/L and 0.5 mg/L, respectively) to week 44 (35.8 kU/L and 0.7 mg/L, respectively) in peanut SLIT subjects.

Adverse Events

Adverse events were reported in all three included studies. In the study by Varshney *et al.*,²⁶ peanut OIT subjects had clinically relevant symptoms after 1.2% of 407 buildup doses during the buildup phase. One sub-

ject treated with peanut OIT experienced mild gastrointestinal symptoms during up-dosing. At OFC, one peanut OIT subject experienced mild upper respiratory symptoms and moderate urticaria. During the study, two OIT subjects required epinephrine at the initial escalation day, and four subjects in the placebo group required treatment with epinephrine at home dosing and OFC.

In the study by Kim *et al.*,²⁵ symptoms were reported with 11.5% of peanut doses and 8.6% of placebo doses. The majority of reactions (9.3%) in those receiving peanuts were transient oropharyngeal itching. Of the 4182 active peanut doses, 11 (0.26%) home doses required treatment with an antihistamine, and one (0.02%) home dose also required albuterol for mild wheezing. None required treatment with epinephrine during the study.

In the study by Fleischer *et al.*,²⁷ a total of 240 adverse events were reported, but 234 were unrelated to the studied product. Most of the adverse events (86%) were judged to be mild in severity and were similar between the SLIT and the placebo groups (36% versus 31%). One dose-related serious adverse event occurred during the buildup stage in a peanut SLIT subject and required treatment with epinephrine.

Using a random effects model, we conducted a meta-analysis to compare the difference in the number of subjects who required epinephrine during the study between SLIT or OIT groups and placebo group. The results showed there is no difference between the two groups (OR, 0.51; 95% CI, 0.03–10.20; Fig. 5).

DISCUSSION

Despite significant ongoing research, the standard of treatment for peanut allergy remains strict avoidance. Allergen-specific immunotherapy is the only long-term treatment option directed toward the causes of IgE-mediated allergic diseases.²⁸ Traditional subcutaneous immunotherapy has proven unsafe for peanut allergy.^{14,15,29} Thus, recent studies on peanut allergy have focused on the efficacy and safety of OIT and SLIT. Although the efficacy of OIT and SLIT for peanut allergy has been shown in a number of small controlled and uncontrolled studies, there are different opinions about whether OIT and SLIT for peanut allergy are clinical procedures.^{21,22}

We performed a systematic review and meta-analysis of the efficacy of OIT and SLIT in patients with peanut allergy. Using a systematic strategy, we performed a search of the published literature for potentially relevant studies. Three small RCTs were identified as being at low risk of bias and were included in the final analysis. In total, 19 patients received OIT, 31 patients received SLIT, and 36 patients received a placebo. Compared with the placebo, the meta-analysis showed the efficacy of OIT and SLIT in patients with

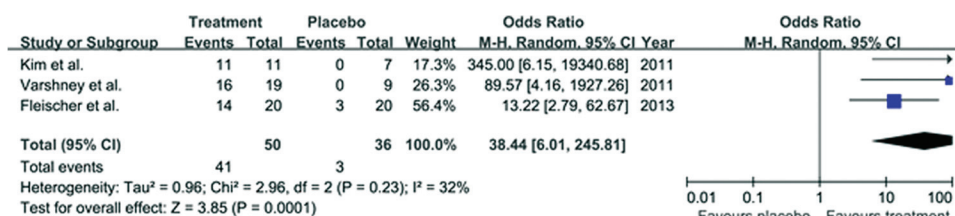


Figure 4. Efficacy of allergen-specific immunotherapy (sublingual immunotherapy [SLIT] or oral immunotherapy [OIT]). Meta-analysis of three randomized control trials (RCTs) in patients passed a defined amount of peanut protein by oral challenge. A random effects model was used to produce the data.

Table 2 *Post hoc* sensitivity analysis (each study excluded)

Excluded Study	Subjects (n)	I ² (%)	OR	95% CI	p Value
Kim <i>et al.</i> ²⁵	68	18	21.61	4.12–113.3	0.0003
Varshney <i>et al.</i> ²⁶	58	55	39.11	1.90–803.57	0.02
Fleischer <i>et al.</i> ²⁷	46	0	147.02	12.80–1687.95	<0.0001

OR = odds ratio; CI = confidence interval.

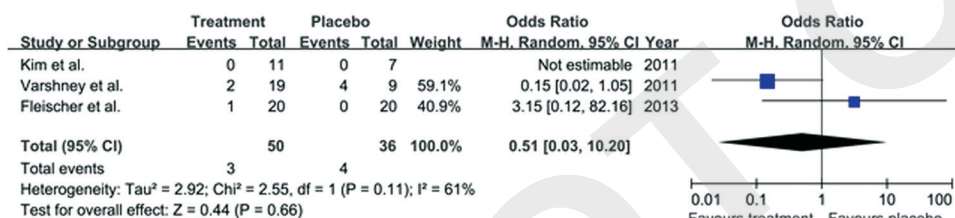


Figure 5. Safety of allergen-specific immunotherapy (sublingual immunotherapy [SLIT] or oral immunotherapy [OIT]). Meta-analysis of three randomized control trials (RCTs) in patients required treatment with epinephrine during the study. A random effects model was used to produce the data.

peanut allergy. The sensitivity analysis indicated the consistent efficacy of OIT and SLIT for peanut allergy. Because only one study of OIT and two studies of SLIT met the inclusion criteria, we did not conduct a subgroup analysis of the efficacy of OIT and SLIT.

Other immunologic changes that are associated with the induction of peanut tolerance were also analyzed in the review. Of the three included studies,^{25–27} compared with patients receiving a placebo, two studies found a decreased SPT size in patients receiving immunotherapy, one study found decreased peanut-specific IgE levels in patients receiving SLIT, and all three studies found increased peanut-specific IgG4 levels in patients receiving immunotherapy. These results indicate that immunotherapy is helpful for the induction of peanut tolerance. The recent study reported that OIT can modify IgE and IgG4 responses to major peanut allergens.³⁰ However, in the study by Fleischer *et al.*,²⁷ peanut-specific IgE levels significantly increased between baseline and week 44 in SLIT subjects. Thus, additional studies are needed to address the effects of peanut-specific immunotherapy on the induction of peanut tolerance.

All three included studies^{25–27} reported adverse events. No fatal or near-fatal adverse events were reported in any of the included studies. Only one dose-related serious adverse event was reported in the study

by Fleischer *et al.*²⁷ We compared the number of subjects who required epinephrine during the study by meta-analysis. No difference was found between the OIT or SLIT groups and placebo group. It indicated that OIT or SLIT did not increase the incidence of severe adverse events. However, children with more severe reactivity have generally been excluded, which limits the extent to which the conclusions can be generalized.

In summary, although we showed a statistically significant benefit of peanut immunotherapy in patients with peanut allergy, the rigorous evidence on this subject only comes from three eligible small RCTs. Therefore, there is currently insufficient evidence for the long-term effectiveness and safety of peanut immunotherapy to recommend its routine use in clinical practice. Additional larger, well-designed, and double-blind RCTs are needed to confirm the efficacy and safety of peanut immunotherapy.

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