

Received Date : 22-Jul-2016

Revised Date : 12-Sep-2016

Accepted Date : 08-Nov-2016

Article type : Regular Article

TITLE PAGE

Double-blind placebo controlled challenge showed that peanut oral immunotherapy was effective for severe allergies without negative effects on airway inflammation

Short title: Peanut oral immunotherapy

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/apa.13668

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FINANCE

AKK and RU received grants from the Foundation for Allergy Research in Finland and the Päivikki and Sakari Sohlberg Foundation and RU also received grants from the Foundation for Pediatric Research in Finland, Allergy and Asthma Federation and the Finnish Society of Allergology and Immunology. Thermo Fisher Scientific provided the kits for the IgG4 analyses. The sponsors had no involvement in any aspect of the study or paper.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

ABSTRACT

Aim: This study examined the efficacy and the safety of peanut oral immunotherapy (OIT).

Methods: We recruited 60 patients aged 6-18 years who had a moderate-to-severe reaction to a double-blind placebo-controlled peanut challenge: 39 received OIT during an eight-month build-up phase and maintenance phase and 21 controls avoided peanuts. We measured specific immunoglobulin E and G4 (IgE and IgG4) to peanuts and to Ara h 1, 2, 3, 8, and 9 and monitored adverse events, bronchial hyperresponsiveness (BHR) to methacholine and fractional concentrations of exhaled nitric oxide (FeNO). The median follow up was 30 months.

Results: Most (85%) of the OIT patients passed the build-up phase and 67% tolerated five grams of peanuts during the post-treatment challenge. No controls were desensitised, with a risk ratio of 29 and 95% confidence interval of 1.9-455. During OIT, IgE to peanut, Ara h 1, 2 and 3 decreased and IgG4 increased. Consuming peanuts had no harmful effects on BHR or FeNO. The annual incidence rate of emergency visits during the follow-up period was 11% or 3.0 per 10,000 patient days.

Conclusion: Peanut OIT was efficacious in severe allergies without negative effects on airway inflammation, but unpredictable long-term reactions might occur.

Key words: Airway inflammation, Ara h 2, Bronchial hyperresponsiveness, Oral immunotherapy, Peanut allergy.

Key notes

- This double-blind, placebo-controlled challenge examined peanut oral immunotherapy (OIT) in 39 patients aged 6-18 years with moderate-to-severe peanut allergy and compared them to 21 controls who avoided peanuts.
- Most (85%) of the OIT patients passed the build-up phase and 67% tolerated five grams of peanuts during the post-treatment challenge.
- OIT had no harmful effects on bronchial hyperresponsiveness and airway inflammation.

INTRODUCTION

Being allergic to peanuts is the most common cause of fatal food-induced anaphylaxis (1), with an increasing prevalence in Western countries (2). Avoidance and medical treatment of allergic reactions are the current methods used to manage a severe peanut allergy.

However, it is difficult to avoid peanuts, as they are widely used in the food industry as they are rich in protein. Even trace amounts can cause severe allergic reactions in the most sensitive patients. Thus, the constant fear of sudden life-threatening reactions significantly impairs the health-related quality of life of the families of children and adolescents with a

severe peanut allergy (3). Unlike other early life food allergies, a peanut allergy is rarely outgrown (4).

Oral immunotherapy (OIT) is a promising option for increasing tolerance in a food allergy (5-8). It might reduce the risk of severe allergic reactions with accidental ingestion and improve food allergy related quality of life (9). However, the long-term safety of OIT has not yet been established and it seems that very few patients develop sustained unresponsiveness after discontinuing the therapy (10). Although the majority of reported adverse reactions during OIT have been mild, severe life-threatening reactions can occur (11). Having a peanut allergy has been associated with greater asthma morbidity and an increased risk for hospitalisation in asthmatic patients (12). It has been argued that asthma control might deteriorate during an OIT (11,13), but evidence is lacking on the effect of continuous ingestion of peanuts by allergic individuals on bronchial hyperresponsiveness (BHR) or airway inflammation.

A severe peanut allergy may be distinguished from asymptomatic sensitisation by component resolved diagnostics. Sensitisation to peanut allergens Ara h 1, 2, 3 and 6 indicates a very severe allergy and low threshold doses, whereas mono-sensitisation to the birch-pollen cross-reactive allergen Ara h 8 indicates mild symptoms or tolerance. Ara h 9 may cause allergic symptoms, especially in the Mediterranean, but its content in peanuts is low (14).

This study aimed to determine the efficacy and long-term safety of a peanut OIT protocol with home-based dose escalations in six to 18-year-old children and adolescents, including those with a history of severe anaphylactic reactions who were particularly high-risk patients. The safety measurements included monitoring adverse symptoms, measuring BHR to methacholine and airway inflammation.

METHODS

Between May 2011 and December 2013, we recruited 60 patients aged 6–18 years with a suspected severe peanut allergy from a referred sample at the Helsinki University Skin and Allergy Hospital, Finland. The patients were eligible if they had a moderate-to-severe reaction at the baseline double-blind, placebo controlled food challenge (DBPCFC). On two non-successive days, each patient received 5, 50, 200 and 1,000mg of peanut protein or a placebo at 30-minute intervals. If mild subjective symptoms emerged, the challenge dose was reduced or the interval was prolonged to 60 minutes. We stopped the challenge if the objective symptoms emerged. We assessed the severity of the reaction by a modified threshold-adjusted score: 1-5 indicated mild, 6-13 moderate and 14-23 severe (Table S1) (14). In addition, six patients who had a recent history of a severe reaction and sensitisation to Ara h 2 (range 27.8 to 365 kU/L) (14,15) continued with avoidance without challenge. We excluded patients who had forced expiratory volume in one second (FEV1) of less than 80%, any major chronic illness, or ongoing immunotherapy. The control patients continued with peanut avoidance. The allocation to the groups was based on the preferences of the patients and parents. The OIT group underwent the eight-month OIT protocol, in which we used a peanut margarine made from roasted defatted peanut flour with 50% protein, 12% fat (Byrd Mill, Virginia, USA) mixed with Keiju 70% soy-free and milk-free margarine (Raisio, Raisio, Finland). From week 20 we used peanuts. The patients received their first dose of 0.1mg peanut protein at the hospital and continued with the same daily dose at home. Dose escalations every one to two weeks occurred at home or during an appointment with a nurse (Table 1). Standard doses of antihistamines were taken daily during the build-up phase. The patients were provided with emergency medication: namely an adrenalin auto-injector, antihistamines and prednisolone. If the patient experienced mild allergic symptoms, the dose increment was postponed until the patient was asymptomatic. If the symptoms were severe, the dose was reduced. Adverse symptoms were collected using weekly symptom diaries, by questions during hospital visits and by phone calls, and graded for severity (16). Exercise was forbidden for one hour after each dose and on the day of escalation. Four weeks after

reaching the maintenance dose, we repeated the DBPCFC. Thereafter, the patients took three to seven weekly doses of four raw or roasted peanuts. Those who failed the challenge continued with the daily dose they could tolerate. The patients were followed annually when symptoms emerged.

We performed skin prick tests (SPTs) with peanut diluted in 0.9% sodium chloride on the child's forearm with a single-tine lancet. Histamine chloride (10 mg/mL) served as the positive control. We considered the SPT to be positive if the wheal size was ≥ 3 mm greater than the negative control solvent (ALK-Abelló, Horsholm, Denmark). The assessments took place at baseline and at the follow-up visits. We measured the complete blood count, serum total immunoglobulin E (IgE) and concentrations of specific IgE and specific immunoglobulin G4 (IgG4) antibodies to peanut and the peanut allergens Ara h 1, 2, 3, 8, and 9 using an ImmunoCAP immunoassay (Thermo Fisher Scientific, Uppsala, Sweden). The detection limits were 0.1 kU/L for specific IgE and 0.07 mg/L for specific IgG4 (19). Before and after the build-up phase, we performed a methacholine challenge test (17) to measure the provocative dose causing a 20% decrease in FEV1 (PD20FEV1) and measured the fractional concentration of exhaled nitric oxide (FeNO) using a standard online method, namely EcoMedics CLD 88 (18). In addition, the patients and their parents filled in food allergy-related quality of life questionnaires (19,20). Growth measurements were converted to standard deviation (SD) scores using PEDIATOR software (Tilator, Säkylä, Finland) and data for Finnish children as the reference (21). The allergenic activity of the peanut flour used in the OIT was confirmed using ISAC 112 IgE-microarray inhibition (Thermo Fisher Scientific, Uppsala, Sweden). Peanut flour extract (1:5 w/v in phosphate buffer) inhibited IgE binding of sera to solid-phase Ara h 1, 2, 3, and 6, but not to 8 or 9 (14).

The primary analyses were intention-to-treat (ITT). Our sample provided 93% power to detect a significant difference in the rate of desensitisation between the study groups at a 5% two-sided significance level. Data were analysed with SPSS, version 22 (SPSS Inc, Chicago, Illinois, USA). The study followed the principals of Declaration of Helsinki. The

ethics committee at the Helsinki University Hospital for Children and Adolescents approved the study protocol. The patient and one of their parents provided informed, written consent. The study was registered at Clinicaltrials.gov (NCT01502878).

RESULTS

In the ITT analysis, 33/39 (85%) OIT patients achieved the daily maintenance dose of four peanuts in a median (range) of 269 (223-486) days and 31 (80%) attended the end of study DBPCFC, as per protocol. The total follow-up was a median (range) of 31 (1.6 to 54) months. The baseline clinical characteristics are shown in Table 2 and Figure 1 illustrates the patient flow and the reasons for discontinuation.

After the eight-month build-up, the amount of peanut protein tolerated at the DBPCFC increased by a median of 22.5-fold from the median (range) of 5mg (<5-255 mg) to 1,255 mg (255–1,255 mg) ($p < 0.001$). We found that 26 patients - 67% in the ITT and 84% in the per protocol analysis - passed the second challenge and tolerated 5g of peanut (1,255 mg protein). None of the 21 control patients on avoidance were desensitised, with a risk ratio of 29 and 95% confidence interval of 1.9–455, $p < 0.001$).

During the OIT, lung function, as measured using FEV1 as a percentage of predicted, did not change from baseline. BHR to methacholine tended to be alleviated, as reflected by an increase of PD20FEV1 from 810 μ g at baseline to 1451 μ g, without an effect on the number of patients with moderate or severe hyper-responsiveness (PD20FEV1 < 600 μ g), but the change did not reach statistical significance. FeNO showed no change, but the number of patients with increased FeNO levels, with a z-score of more than 1.96, tended to decrease ($p = 0.08$) (Table 3). The blood eosinophil counts remained stable and growth was similarly normal in both of the study groups.

The peanut SPT diminished in the OIT group, but did not diminish in the avoidance group. OIT lacked a significant effect on specific IgE to peanut Ara h 1, 2, 3, 8, or 9, but specific IgG4 to peanut, Ara h 1, 2, and 3 increased significantly (Table S2). At the end of the build-up phase, the increase in Ara h 2-specific IgG4 was greater in the 26 successfully desensitised patients compared to the 13 treatment failures, with a median of 8.1 (0.01–249 mg/l) versus 0.91 (-0.07–39.8) ($p=0.005$). No changes were observed in the avoidance group. In the 29 patients who continued OIT at the one-year follow-up, specific IgE to peanut Ara h 1, 2, and 3 decreased significantly ($p<0.001$) (Figure 2).

During the build-up phase, 30/39 (77%) of the OIT patients reported adverse symptoms and 16/39 (41%) needed additional antihistamines, 15/39 (38%) took prednisolone and one/39 (2.6%) used the adrenalin autoinjector. During the build-up phase, five adverse events led to emergency medical contact, which equated to a rate of 4.6 per 10,000 patient days. During the whole follow-up period, 11/39 (28%) patients sought emergency medical advice at a rate of 3.0 per 10,000 patient days. In one 11-year-old male patient, the 800 mg maintenance dose caused an unexpected serious anaphylaxis, including generalised urticaria, hypotension and desaturation. He was treated at the emergency room with adrenalin, oxygen and fluid therapy 90 minutes after the onset. The risk factors for his severe reaction were vigorous exercise, delayed administration of adrenalin and neglecting previous alarming signs. Alcohol use preceded symptoms in one teenager (Table 4).

During the eight-month build-up phase, the patient-reported food allergy-related quality of life score improved in the OIT patients ($p=0.03$). The same did not occur for the caregivers. In the longer term, the patient-reported food allergy-related quality of life score showed no further improvement, (Table 3).

During the 2.5-year follow-up, 28/39 (72%) of the patients consumed 100mg to 2g peanut protein on two to seven days weekly and 20/26 (77%) of the responders adhered to the 800mg dose as per protocol. The median (range) weekly protein consumption was

5,600mg (1,050-5,600mg). The reasons for discontinuing the treatment after the build-up phase were non-compliance in two cases and adverse symptoms in four cases.

DISCUSSION

We found that OIT increased the threshold dose and induced desensitisation better than avoidance in cases of severe peanut allergy: 67% were desensitized in the ITT and 83% in the per-protocol analysis. The median tolerated dose increased 22.5-fold, from 5-1,255 mg peanut protein, which corresponded to six to seven peanuts. The proportion of desensitised patients (67%) in the present study agreed with the 67% desensitisation rate in six to 17-year-old children who underwent a six-month peanut OIT (7).

To the best of our knowledge, this study evaluated the safety of OIT for the first time, by measuring BHR and airway inflammation. We showed that continuous consumption of peanuts by allergic individuals resulted in no harmful effects on BHR or airway inflammation. Poorly controlled asthma is the most important risk factor for fatal and near-fatal anaphylactic reactions to food (1) and it has been argued that asthma control might deteriorate during an OIT (11,13). We showed that, with careful evaluation of asthma control throughout the treatment, continuous consumption of peanuts by allergic individuals resulted in no harmful effects on airways.

The safety profile of our home-based, up-dosing regimen, with a very low 0.1mg protein initial dose that differed from other published protocols was acceptable. Most patients reported mild symptoms of peanut intake during the eight-month build-up phase. Gastrointestinal complaints occurred frequently in the beginning, but declined in the longer term. Only one child received adrenaline, similar to a previously reported rate with hospital-based dose increments (7).

In the 2.5-year follow-up, 51% of the patients fully adhered to the treatment.

Similarly, other studies showed that 50% of the children who started milk OIT were consuming milk daily at 2.5-year and seven-year follow-ups (22,23). The 60% full adherence of the patients who achieved the maintenance dose in this study must be considered together with the incidents of unexpected moderate-to-severe reactions that led to emergency contacts. The 8% annual incidence rate for emergency medical contact during the maintenance phase was relatively high, but, with the inclusion of anaphylactic patients in the study, it is not surprising. The risk factors for life-threatening anaphylaxis during OIT are adolescent age, suboptimal asthma control and failing to heed alarming signs, which should have led to earlier OIT discontinuation (11). Likewise, we were able to identify that exercise, emotional stress, alcohol, non-adherence and failure to use an adrenalin injector in an emergency increased the severity of unexpected reactions. To improve long-term safety, the patient's adherence should be monitored carefully and the treatment should be stopped in the presence of alarming signs.

Despite the adverse events, the patients reported improvements in food allergy-related quality of life. Previously, quality of life improved during peanut OIT when parents assessed their children and when children and teenagers assessed themselves (9). We did not follow quality of life in the avoidance group and whether improved quality of life persisted and was related to OIT or to other factors such as better guidance and follow up remains to be determined.

Whether OIT results in sustained tolerance is controversial. Although OIT to eggs resulted in desensitisation in 75% of patients in a previous study, only 28% were considered to have sustained unresponsiveness after discontinuing the treatment (6). Ara h 2-negative patients, whose peanut allergy was not confirmed by a challenge at baseline, developed tolerance during a five-year follow-up. In the same study, the majority of the Ara h 2-sensitised true peanut-allergic patients failed to develop sustained unresponsiveness (10). The increase of specific IgG4 agrees with previous studies. Specific IgE decreased at the

one-year follow up, and not before, which may be explained by the fact that during an OIT, specific IgE initially increases, but decreases in the longer term (24).

The strength of our study was the baseline DBPCFC for every OIT patient irrespective of the specific IgE concentrations and history of anaphylaxis. Because not all peanut-sensitised patients are symptomatic, the exclusion of tolerant patients at baseline is of the utmost importance. The major limitation of our study was the lack of random allocation to the groups. The comparison of the outcomes should be interpreted in the light that patients with lower morbidity might have decided to continue avoidance. However, all patients were obviously sensitised to Ara h 2, which is the best indicator of a severe peanut allergy and predicts systemic reactions (14).

CONCLUSION

Our study showed that OIT was effective and relatively safe for a severe peanut allergy and might improve food allergy-related quality of life in selected patients. However, not all patients were safely desensitised. If particular attention was paid to asthma control, OIT did not have a harmful effect on BHR or airway inflammation. The benefits and long-term compliance should be carefully evaluated at an individual level and the treatment should remain restricted to specialist centres. More studies regarding long-term safety and quality of life are needed. For additional safety improvements, OIT should be further developed using new protocols and vehicles for dosing.

Acknowledgements

We thank Ms Helena Voutilainen for planning and organising the manufacture of the peanut margarine, Ms Jonna Harain for monitoring the patients and Mr Anssi Koivuselkä, Ms Leena Lahti and Ms Leena Riittinen for their contributions to the laboratory analyses.

ABBREVIATIONS

BHR, Bronchial hyperresponsiveness

DBPCFC, Double-blind placebo-controlled peanut challenge

FeNO, Fractional concentration of exhaled nitric oxide

FEV1, Forced expiratory volume in one second

IgG4, Immunoglobulin G4

ITT, Intention to treat

IgE, Immunoglobulin E

OIT, Oral immunotherapy

PD20FEV1, Provocative dose causing a 20% decrease in FEV1

SD, standard deviation

SPT, Skin prick test

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Table 1. Peanut oral immunotherapy protocol in children and adolescents with severe peanut allergy

Build-up phase: daily dose of antihistamine		
Week	Up-dosing at home, unless otherwise indicated	Daily intake of peanut protein (mg)
1	Hospital (nurse)	0.1
2		0.2
3		0.4
4	Hospital (nurse)	1
6		2
8		3
10	Hospital (nurse)	5
12		6
14	Hospital (nurse)	10
16		25
18		50
20	Hospital (Pediatric allergist)	0.25 peanut ~50
22	Hospital (nurse)	0.5 peanut ~100
24		0.75 peanut ~150
26		1 peanut, ~200
28	Hospital (nurse)	1.5 peanuts ~300
30		2 peanuts ~400
32	Hospital (nurse)	3 peanuts ~600
34		4 peanuts ~800
DBPCFC, blood tests, skin prick tests, methacholine challenge, exhaled NO, Quality of life questionnaire		
Maintenance phase: 3–7 weekly doses of 4 peanuts		

^aDBPCFC, double-blind placebo-controlled food challenge 1,255 g peanut protein; ^bNO, nitric oxide; ^cQuality of life

Table 2. Baseline characteristics of the study children and adolescents

	OIT n = 39	Avoidance n = 21	p value
Male gender	22 (56)	13 (62)	0.78
Age (years)	8.3 (6.3–18.6)	8.6 (6.0–13.7)	0.99
Asthma, doctor-diagnosed	27 (69)	13 (62)	0.38
Inhaled corticosteroids	27 (69)	13 (62)	0.38
Atopic eczema	26 (67)	18 (86)	0.14
Other food allergy	24 (62)	13 (62)	1.00
Rhinitis	26 (67)	18 (86)	0.11
Specific IgE (kU/L)			
Peanut	74.6 (1.80–1820)	66.2 (0.90–876)	0.50
Ara h 1	16.6 (0.01–608)	10.3 (0–293)	0.36
Ara h 2	43.5 (0.60–699)	31.5 (0.30–365)	0.44
Ara h 3	3.55 (0.01–261)	1.29 (0.01–62.7)	0.45
Ara h 8	7.48 (0–216)	8.51 (0–369)	0.87
Ara h 9	0.04 (0–31.1)	0.03 (0–10.2)	0.50
Peanut skin prick test (mm)	10 (6–18)	10 (5–28)	0.99
Serum total IgE (kU/L)	676 (95–4458)	759 (89–11 182)	0.63
Blood eosinophil count	0.54 (0.17–1.44)	0.37 (0.02–1.43)	0.11
Sensitized ^a to birch-pollen	34 (87)	19 (90)	1.00
Baseline DBPCFC ^b			
Peanut protein tolerated (mg)	5 (0–255)	255 (0–255)	0.008
Severity score ^c	13 (9–22)	11 (9–22)	0.31
Adrenalin ≥1 dose	21 (54)	11 (73)	0.51
≥2 doses	11 (28)	3 (20)	

^aSpecific-IgE ≥0.35 kU/L, ^bDBPCFC, double-blind placebo-controlled food challenge, ^cReferences in (14). *P* values were determined using Pearson's chi-square, Fisher's exact or Mann-Whitney U tests. The values are reported as n (%) or median (range).

Table 3. Lung function (FEV1), provocative dose of methacholine causing a 20% decrease in FEV1 (PD20FEV1), fractional concentration of exhaled nitric oxide (FeNO), and food allergy related quality of life scores in patients receiving peanut oral immunotherapy (OIT).

Methacholine challenge (n = 33)	Baseline	At 8 months	p value
FEV1 (% predicted)	98.6 (72.3–119.8)	95.6 (78.5–110.5)	0.14
PD20FEV1 (μg)	810 (18 to >2600)	1451 (43 to >2600)	0.27
PD20FEV1 <600 μg	13 (40)	14 (42)	1.00
Exhaled nitric oxide (NO) (n = 35)			
Exhaled NO (ppb)	19.5 (4.6–130.8)	15.8 (3.4–134.4)	0.24
Exhaled NO z-score >1.96	22 (63)	14 (40)	0.08
Food allergy related quality of life scores			
Patients ^a (n=27)	57 (1-109)	40 (15-101)	0.03
Caregivers ^b (n=26)	16 (0-56)	14 (1-51)	0.58

Number of patients, ^a27, and ^b26. Calculated using Wilcoxon Signed-Rank or McNemar tests. Values are reported as n (%) or median (range). In one patient, asthma was diagnosed after the baseline tests, before starting the treatment.

Table 4. Adverse events in patients receiving peanut oral immunotherapy

	Build-up (n=39)	Maintenance (n=34)
Adverse symptom n (%)		
Abdominal pain	16 (41)	6 (18)
Vomiting	4 (10)	2 (6)
Nausea	5 (13)	2 (6)
Wheezing or dyspnea	10 (26)	7 (21)
Skin rash/eczema/flare	17 (44)	6 (18)
Urticaria	9 (23)	8 (24)
Anaphylaxis	0	2 (6)
Treatments^a n (%)		
Emergency contact	5 (13)	6 (18)
Adrenalin	1 (3)	3 (9)
Intensive care admission	0	0
Severity^b of symptoms		
0	11 (28)	17 (50)
I	9 (23)	2 (6)
II	7 (18)	2 (6)
III	4 (10)	3 (9)
IV	8 (20)	9 (26)
V	0	0

^aNone of the patients received the treatment more than once. ^bSeverity of symptoms adopted from (16).

Figure 1. Flow diagram of patient enrolment and retention

Figure 2. Specific IgE responses to peanut, Ara h 1, 2, and 3 in the oral immunotherapy patients



