doi: 10.1111/j.1365-2222.2011.03699.x
Clinical & Experimental Allergy, **41**, 1273–1281

ORIGINAL ARTICLE **Clinical Allergy**

Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome

K. Anagnostou[1], A. Clark[2,3], Y. King[2], S. Islam[1], J. Deighton[2] and P. Ewan[2]
Departments of [1]Medicine, Box 157 [2]Allergy, Box 40 and [3]Paediatrics, Box 181 Addenbrooke's Hospital, University of Cambridge, Cambridge, UK

Clinical & Experimental Allergy

Summary

Background Peanut allergy is severe and rarely resolves.
Objective To test the efficacy and safety of a new oral immunotherapy (OIT) protocol for peanut allergy.
Method Twenty-two peanut-allergic children underwent oral challenge. OIT was administered by gradual updosing with 2-weekly increments (8–38 weeks) to 800 mg of protein (5 peanuts/day) followed by 30-week maintenance. Oral challenge was repeated after 6 and 30 weeks maintenance.
Results Twenty-two children (median 11 years) had positive challenges (threshold 1–110 mg). Nineteen of 22 (86%) tolerated updosing and maintenance at 800 mg protein/day. One of 22 dropped out; 2/22 tolerated updosing and maintenance at 200–400 mg protein. Reactions, mostly mild, occurred in 86% during immunotherapy, adrenaline was not required. Eight of 8 with pre-immunotherapy peanut IgE < 27.3 kU/L required no dose adjustment compared with 5/13 with pre-immunotherapy peanut IgE $\geqslant 27.3$ kU/L. Twelve of 22 (54%) required a transient dose reduction because of reactions possibly related to extrinsic factors: tiredness, infection and exercise. After 6 weeks, 12/22 (54%) had no reaction to a 2.6 g protein challenge. After 30 weeks, 14/22 (64%) tolerated 6.6 g protein. The median tolerated peanut dose increased 1000-fold following immunotherapy, from 6 to 6459 mg of protein.
Conclusions and Clinical Relevance We used a novel protocol using gradual updosing, and higher maintenance dose resulting in a better outcome compared with rush protocols. There was a 1000-fold increase in the amount of peanut tolerated with a good safety profile. No serious adverse events occurred. Most subjects tolerated five peanuts and all were protected against amounts likely during accidental ingestion. New information is provided on 'extrinsic factors', updosing method and factors associated with success (trial registration http://ClinicalTrials.gov – ID number NCT01259804).

Keywords allergy, desensitization, oral immunotherapy, peanut anaphylaxis
Submitted 5 August 2010; revised 28 October 2010; accepted 14 December 2010

Correspondence:
A. Clark, Department of Allergy, Box 40, Addenbrooke's Hospital, University of Cambridge, Cambridge CB2 0QQ, UK.
E-mail: atclark@doctors.org.uk
Cite this as: K. Anagnostou, A. Clark, Y. King, S. Islam, J. Deighton and P. Ewan, *Clinical & Experimental Allergy*, 2011 (41) 1273–1281.

Introduction

Peanut allergy is common, affecting 1–2% of young children in Europe and the United States [1–3], and unlike other common childhood food allergies (e.g. to hens egg), resolution is uncommon [4]. The quality of life of the affected families is reduced because of constant fear over food choices and the likelihood of anaphylaxis [5, 6]. Despite the current best management, families of peanut-allergic children have poor knowledge of how to avoid and also treat food allergy emergencies [7]. Accidental reactions are common (annual incidence rates for accidental reactions of 3%, 14% and 50% have been reported in large studies [8]). Nearly one-third of nut-allergic children cannot recognize the nut to which they are allergic – this lack of recognition puts them at an increased risk of unintentional ingestion [9]. There is a need to develop a disease-modifying therapy for peanut allergy. Immunotherapy for inhalant and stinging insect allergy by subcutaneous injection has proven efficacy and safety. An early study of subcutaneous immunotherapy for peanut allergy showed a trend to benefit but was terminated after a severe adverse reaction [10]. Oral immunotherapy (OIT) for the treatment of persistent hen's

egg and cow's milk allergy has been studied [11, 12]. Sublingual immunotherapy with hazelnut extract was studied in a small group of subjects with hazelnut allergy demonstrating an increase in dose threshold [13]. Two recently published studies of peanut OIT using an initial rush protocol showed poor tolerability of the rush period, with better efficacy after a period of gradual dose escalation [14–16]. We reported previously the use of OIT as a treatment for peanut allergy in four children, demonstrating that desensitization to peanut can be achieved [17]. We now report the follow-up data using a gradual dose escalation and high top-dose protocol in those four and a further 18 children, to examine efficacy and safety in more detail.

Method

This is an uncontrolled clinical trial of 22 peanut-allergic children treated with high-dose OIT using a slow updosing protocol and standardized follow-up. The study was approved by the Local Ethics and Research and Development Committees and was funded by a local medical charity, The Evelyn Trust. The trial had been registered and published at http://ClinicalTrials.gov (ID number NCT01259804). Each family gave written informed consent. All investigations were performed at the Cambridge Biomedical Research Campus, UK. Participants approached us after reading about the study in a national patient support group newsletter (Anaphylaxis Campaign http://www.anaphylaxis.org). They were enrolled in order of presentation. Inclusion criteria were a positive peanut oral challenge and the presence of peanut-specific IgE in children aged 4–18 years. Major immunodeficiency and an inability to comply with the study protocol were exclusion criteria. Twenty-two children were enrolled. Children with a history of anaphylaxis after peanut ingestion were included.

Skin prick tests (SPTs) were performed (peanut extract, saline negative and histamine 10 mg/mL positive controls; single point lancets; ALK-Abello, Hørsholm, Denmark) and peanut SPT was interpreted as positive when the weal diameter was at least 3 mm greater than the negative control. Serum was analysed for whole peanut and Ara h 2-specific IgE (CAP-system FEIA; Phadia, Uppsala, Sweden).

Double-blind placebo-controlled food challenges

Double-blind placebo-controlled food challenges (DBPCFCs) (low-dose challenge protocol) were performed according to an international consensus statement [18]. Peanut was administered as ground and partially defatted peanut flour (50% protein, light roast; Golden Peanut Company, Alpharetta, GA, USA). The carrier was a chocolate bar (32% fat) containing vegetable oil, sugar and orange essence (free of egg, milk, peanut, tree nuts and soya) and blinding was assured by a tasting panel. Placebo and active (peanut flour) doses were administered on separate days in random order, and dose intervals were at least 30 min. A challenge dose regimen including 1, 5, 50 and 500 mg of peanut protein was piloted for the first subject. The dose range was subsequently modified to 1, 5, 25, 50, 75 and 100 mg of peanut protein. The challenge was scored positive if (a) objective symptoms occurred or (b) subjective symptoms occurred on at least two consecutive doses. A negative DBPCFC was followed by an open challenge with a cumulative dose of six peanuts (approximately 900 mg protein). Overall, the challenge was scored negative if there was no reaction to the DBPCFC or open challenges [18]. Pre-intervention challenges were used to both confirm the presence of clinical allergy to peanut and identify the highest amount of protein tolerated before a reaction occurred (highest tolerated dose).

Oral immunotherapy

OIT was administered in two phases; firstly, there was a gradual updosing phase with 2-weekly increments to 800 mg/day, followed by a maintenance phase where the highest tolerated dose (with a target of 800 mg/day) was taken continuously for 30 weeks. The same peanut flour used in the challenges was also used for updosing. The updosing phase increments were 0.5, 1, 2, 5, 12, 25, 50, 100, 200, 400 and 800 mg of peanut protein. Starting doses for immunotherapy were below the subject's own pre-OIT threshold. All dose increases occurred in the Wellcome Trust Clinical Research Facility and subjects were observed for 2 h. The same dose was administered at home daily for 2 weeks. At the final updose, subjects were given the choice of continuing to take peanut flour or five to seven peanuts daily (~800 mg protein).

Participating families were advised to record and report any symptoms that occurred during the course of the intervention. Families were provided with oral antihistamines, an epinephrine auto-injector and a treatment plan, with training [8]. Participants were asked to avoid any other source of peanut in their diet. Children were asked to take their dose with food and instructed not to exercise for 1–2 h after taking a dose. Families had 24 h access to the study team by telephone. If reactions occurred that were troublesome, the OIT dose was reduced to the previously tolerated dose for 1–2 weeks before being increased again. Reactions were recorded and categorized according to a published grading system [8].

Post-oral immunotherapy challenges

An open peanut challenge using weighed roasted peanuts was performed after completing 6 weeks of the

maintenance phase (2.6 g peanut protein – dose intervals: 0.8, 0.45, 0.45, 0.45, 0.45 g protein; a total of approximately 12 peanuts). A further peanut challenge was undertaken after completing 30 weeks of the maintenance phase (6.6 g protein – eight equal dose intervals of 0.83 g protein; a total of approximately 32 peanuts). Dosing intervals were 20–30 min and the same criteria for scoring the challenges were used as for the pre-OIT challenge.

Statistics

Medians of non-parametric data sets were compared with the Mann–Whitney *U*-test. Means of normally distributed data were compared with Student's *t*-test. Comparison between multiple non-parametric data sets was made with the Kruskall–Wallis test and Dunn's post-test comparison. Wilcoxon's ranked-pairs test was applied to paired non-parametric data. Data were analysed using Graphpad Prism (v5.0; San Diego, CA, USA).

Results

Study population

Twenty-two children aged 4–18 years were enrolled, with a median age of 11 years. Demographic features are summarized in Table 1.

Pre-immunotherapy peanut challenge

All 22 subjects had a positive DBPCFC (for explanation of subject flow see Fig. 1). The highest tolerated dose of peanut varied between 1 and 110 mg protein (median 6 mg – see Table 2). Subject 12 had anaphylaxis during DBPCFC. He developed rhinitis nausea, breathlessness, tightness in the chest, pallor and severe abdominal pain. He was promptly treated with intramuscular epinephrine, intravenous chlorphenamine and hydrocortisone. Four subjects passed the initial DBPCFC but they all developed objective symptoms during subsequent open peanut challenge. There were no screening failures.

Table 1. Clinical characteristics of participants

Male : female ratio	1	
Age at first peanut reaction	2 years (0.3–7 years)	
Age at enrollment	11 years (4–18 years)	
Other allergic disease	Active (%)	Outgrown (%)
Asthma	64	9
Rhinitis	45	5
Eczema	36	45
Egg allergy	9	36
Milk allergy	5	23
Severity of worst reaction	Mild	23%
before enrollment	Moderate	36%
	Severe	14%
	Unclassified*	27%

Numbers are median (range) unless otherwise specified. Age is shown in years.

*Clinical details insufficient to classify.

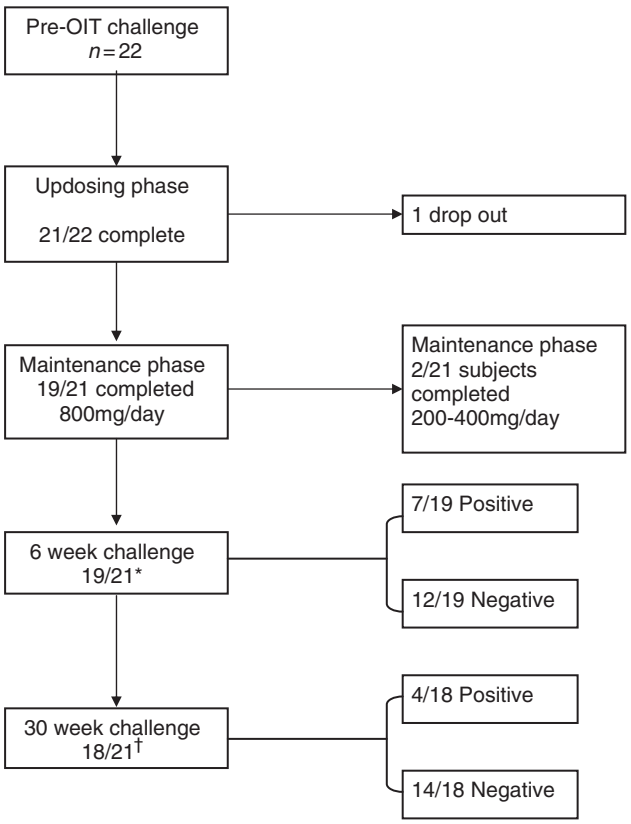

Fig. 1. Subject flow diagram. Subjects continued on maintenance immunotherapy at 6 and 30 weeks challenge time-points. *At 6-week challenge: $n = 3$ not challenged; $n = 1$ drop out; $n = 2$ could not tolerate 800 mg peanut protein OIT maintenance. †At 30-week challenge: $n = 4$ not challenged, $n = 1$ drop out, $n = 1$ had not completed the dose range for the 6-week challenge and $n = 2$ could not tolerate 800 mg peanut protein OIT maintenance. OIT, oral immunotherapy.

Oral immunotherapy

Updosing phase. OIT updosing was commenced in 22 subjects, with 19 tolerating updosing to the planned maximum dose of 800 mg of protein/day (Fig. 1). The amount of time required for updosing was 56–264 days (median 140 days) and the mean number of attendances for updosing was 9.7 (95% CI 8.3–11.1). Eight of 22 (36%) required a transient dose reduction during updosing but were able to complete the schedule up to 800 mg of protein as planned. One subject dropped out after the first updose at home, having developed transient abdominal pain. There was no further contact. During updosing, six subjects reported failure to take a dose. A total of 10 doses were missed on nine separate occasions. No reactions occurred following missed doses.

Table 2. Pre-OIT total peanut and Ara h 2-specific serum IgE (kU/L), maximum tolerated dose pre- and post-OIT (mg), starting dose of OIT (mg) and number of transient dose reductions during OIT for each subject

Subject number	Peanut-specific IgE (kU/L)	Ara h 2-specific IgE (kU/L)	Maximum-tolerated dose pre-OIT (mg)	Pre-OIT challenge symptoms*	Starting dose of OIT (mg)	Maximum-tolerated peanut after OIT (mg)	Number of transient dose reductions during OIT
1	253	70.4	81	OI, TC, A, U, AP, N	5	3278	3
2	3.81	0.57	75	TC, AP	1	6354	0
3	5.17	2.91	110	OI, RC	5	6602	0
4	27.3	21.0	1	OI, RC	0.5	6574	2
5	46	21.3	1	OI, A	0.5	6886	0
6	29.7	15.8	6	OI, AP	1	6503	2
7	3.49	0.38	6	OI, RC, A, AP	1	6486	0
8	6.44	3.73	81	AP	25	7510	0
9	16.1	5.25	75	OI, E, U, AP, N	50	5674	0
10	287	>100	31	OI, E, AP, N	5	6663	2
11	1.54	1.41	1	OI	0.5	6801	0
12	194	NA	56	SOB, N, AP	6	6411	4
13	433	>100	1	OI, A, E	0.5	2485	0
14	395	>100	1	OI, E	0.5	2443	0
15	77.0	75.3	1	OI, TC	0.5	6250	0
16	4.25	NA	55	OI, E	5	6654	0
17	31.3	29.1	1	OI, RC, AP, N, V	0.5	800	2
18	0.41	<0.35	100	OI, TC, AP	5	6459	0
19	65.1	53.6	6	OI, TC, AP, V	0.5	6500	0
20	354	NA	1	OI	0.5	800	9
21	800	>100	81	RC, AP, V	5	800	7
22	14.3	NA	81	Dropout	25	Dropout	Dropout

*All symptoms occurred on active challenge arm. There were no placebo reactions.

NA, not available. Challenge symptoms: OI, oral itching; TC, throat closing; A, angioedema; U, urticaria; E, erythema; AP, abdominal pain with significant change in behaviour; N, nausea; V, vomit; SOB, short of breath; W, wheeze; RC, rhinoconjunctivitis; OIT, oral immunotherapy.

Maintenance phase

Nineteen of 22 (86%) subjects successfully maintained desensitization at the maximum dose of 800 mg of protein for the remainder of the study (Fig. 1). Subjects 20 and 21 initially received 800 mg of protein but subsequently required lower maintenance doses of 400 and 200 mg, respectively, after developing repeated transient episodes of oral itching and abdominal pain. These lower doses were well tolerated for the remainder of the study (30 weeks). Both subjects had high peanut-specific IgE and also had protracted intercurrent illnesses during updosing and maintenance phases. The difficulty in desensitization did not appear to be related to the threshold dose. Overall, there was no difference in median pre-OIT challenge threshold between those who required dose adjustments during OIT (and were more 'difficult' to desensitize) compared with those who did not.

6-week challenge

After completing 6 weeks of the maintenance phase, 19/22 (86%) subjects underwent challenge to 2.6 g of protein. Eighteen of 19 (95%) ingested the full challenge dose, of those 12/19 (63%) had no symptoms and 7/19 (37%) developed mild/moderate symptoms. Symptoms included abdominal discomfort, rhinitis, facial erythema and lip angioedema. Subject 13 developed abdominal pain and the challenge was stopped at the request of the participant, after they had ingested 600 mg of protein. Subjects 21 and 22 were not offered a challenge because they were not receiving the top maintenance dose (Fig. 1).

30-week challenge

After completing 30 weeks of the maintenance phase, 18/22 (81%) subjects underwent a 6.6 g protein challenge. Fourteen of 18 (78%) subjects did not have any symptoms during the challenge. Four of 18 (22%) experienced mild/moderate symptoms (mild abdominal discomfort and vomiting) having ingested all challenge doses. Subjects 13, 20 and 21 were not offered a challenge because they had either not passed the 6-week challenge or were not receiving the top maintenance dose.

Change in tolerated dose after immunotherapy (Fig. 2)

The median highest amount of peanut tolerated during the pre-OIT challenges was 6 mg (range 1–110 mg). After

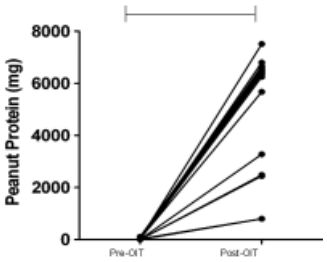

Fig. 2. Change in tolerated dose of peanut protein after immunotherapy, comparing the highest tolerated dose of peanut protein during the pre-OIT challenge to the highest amount tolerated during challenges, after OIT. Results from 21 patients who completed immunotherapy are shown. *Wilcoxon's matched-pairs test (two-tailed). OIT, oral immunotherapy.

updosing and maintenance, the median highest tolerated dose during challenge (or immunotherapy if no challenge was applied) was 6469 mg (range 800–7510 mg). For those who underwent immunotherapy, this represents at least a 1000-fold increase in the median tolerated dose for the group.

Reactions during immunotherapy

Nineteen of 22 (86%) subjects developed transient allergic symptoms at some point during the updosing and maintenance phases. Allergic symptoms did not occur with every dose increase. The mean number of updosing periods where allergic symptoms occurred was 5.2 (95% CI 3.39–7.15), i.e. in about half the updosing periods. The most common symptoms during the updosing phase were by far oral itching (14/22 64%) and/or abdominal pain (50%), whereas less often rhinoconjunctivitis (27%), wheeze (22%), nausea and vomiting (18%) occurred (see Table 3). The majority of symptoms developed within 1 h of taking the dose, lasted <1 h and responded well to oral antihistamines and/or β_2-agonists. Three of 22 (14%) subjects did not have any symptoms during the updosing period.

Reactions with extrinsic factors

During updosing, 12/22 (54%) experienced unexpected transient and isolated reactions to a daily dose that had been taken for up to 2 weeks without reaction (Table 4). The episodes were transient, usually lasting <1 h and would occur on a single day, with the same dose being taken without reaction on subsequent days. These reactions with extrinsic factors (REFs) occurred over a median period of 3.7 months from the start of immunotherapy (range 1.5–6.3 months).

Symptoms were usually mild/moderate and episodes were treated with antihistamines and/or inhaled β_2-agonists (Table 4). Intramuscular epinephrine was not required. REFs were associated with recognizable extrinsic factors such as exercise (up to 2 h after taking a dose), infection (respiratory, varying from a cold to pneumonia or gastrointestinal), tiredness (caused by sleep deprivation), co-exposure to other allergens (i.e. pet dander), anxiety and/or menstruation (Table 4).

Table 3. Symptoms experienced and treatment administered during gradual build up and maintenance OIT expressed as the total number of episodes and as a percentage of the total number of OIT doses administered during each period

	Updosing phase		Maintenance phase	
	n	%	*n*	% ($\times 10^{-2}$)
Total number of doses	2920		5406	
Symptoms				
Sore throat	14	0.5	0	0
Erythema	3	0.1	3	0.05
Urticaria	4	0.1	17	0.3
Angioedema	7	0.2	1	0.02
Conjunctivitis	7	0.2	0	0
Rhinitis	11	0.4	0	0
Cough	0	0	2	0.04
Wheeze	11	0.4	17	0.3
Oral itching	138	5	40	0.7
Nausea	32	1	2	0.04
Vomiting	19	0.7	0	0
Abdominal pain	115	4	31	0.6
Treatment				
None	104	4	27	0.5
AH alone	213	7	53	0.9
Inhaled salbutamol alone	1	0.04	1	0.02
AH+inhaled salbutamol	10	0.4	16	0.3
IM adrenaline	0	0	0	0

The updosing OIT phase lasted from initiation of immunotherapy until a dose of 800 mg of protein was reached. The maintenance phase includes all subsequent doses until the 30-week challenge (note the percentages for the maintenance phase are expressed as $\times 10^{-2}$). Specific treatment administered is also shown.
AH, oral antihistamines; IM, intramuscular; OIT, oral immunotherapy.

Skin prick tests and serum-specific immunoglobulin E levels

There was a significant reduction in SPT weal size to peanut extract at 6 and 30 weeks compared with the baseline (Fig. 3a median 6 vs. 5 vs. 8.5 mm, respectively). The median serum peanut-specific IgE for the group showed a transient rise midway through OIT (38.3 kU/L), followed by a trend to reduction at 30 weeks (8.35 kU/L), compared with the pre-OIT value (29.7 kU/L) (Fig. 3b). Pre-OIT peanut IgE was compared with the 'difficulty' in performing immunotherapy for each individual (measured as the number of episodes of dose reduction during

Table 4. Episodes of reactions provoked by OIT combined with extrinsic factors (REFs)

	Extrinsic factors							
Subject #	Infection or other intercurrent illness	Exercise	Tiredness	Anxiety	Aero-allergen co-exposure	Menstruation	Total number of episodes	Symptoms
1		1			2		3	RC, W
4	1		3	1			5	OI, W, SOB
5			1				1	OI
6	1	1	>5				>5	AP, V, A
7			5				5	AP, RC, OI
12				1			1	AP, W
14	4						4	OI, AP, W
15	>5						>5	OI
17	1		>5				>5	AP, N
19	1	4	2				>5	W, V
20	>5		2	>5			>5	OI, AP
21	>5		1			3	>5	AP,U,W

Subjects experiencing transient symptoms due to extrinsic factors (infection/underlying illness, exercise, tiredness, anxiety, aeroallergen exposure), total number of episodes of reactions with extrinsic factors for each subject and symptoms occurring during those episodes. 'Tiredness' is defined by reduced sleep duration on the previous night/nights. Subject 21 had three episodes of reaction during three consecutive menstrual periods.

OI, oral itching; AP, abdominal pain; W, wheeze; N, nausea; V, vomiting; A, angioedema; RC, rhinoconjunctivitis; U, urticaria; OIT, oral immunotherapy.

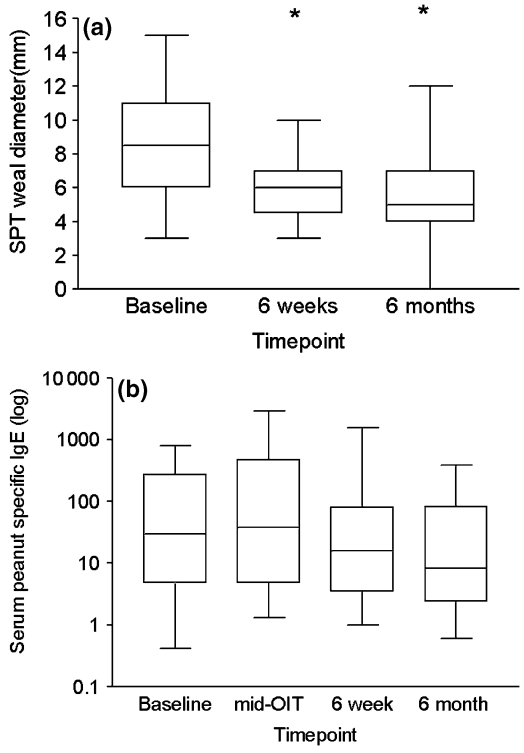

Fig. 3. Skin prick tests (SPTs) and serum IgE. Results of (a) *in vivo* and (b) *in vitro* testing before, during and after oral immunotherapy (OIT). Peanut SPT weal size (mm), serum total and peanut-specific IgE are shown. Statistical analysis was performed using the Kruskal–Wallis test with Dunn's post-test comparison ($^*P<0.05$).

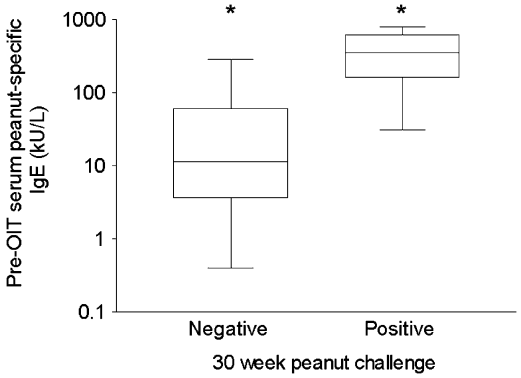

Fig. 4. Serum peanut-specific IgE measured before OIT for those with a negative 30-week peanut challenge ($n=14$; 6.6 g peanut protein) compared with those who had positive challenge or did not undergo challenge ($n=4$ – due to sub-optimal tolerance). The difference between medians for both groups is significant (11.3 vs. 354.0 kU/L; $^*P=0.0025$; Mann–Whitney test). The *Y*-axis is log transformed.

OIT – Table 2). We found that no subject (8/8) with a peanut IgE < 27.3 kU/L required an alteration to their immunotherapy regimen. In contrast, 5/13 (39%) with a peanut IgE ≥ 27.3 kU/L required a dose reduction ($P=0.0068$; Fisher's exact test). In addition, median pre-OIT serum peanut IgE was significantly lower in those who passed the 30-week challenge ($n=14$) compared with those who failed ($n=4$) or did not attempt it due to reduced tolerance ($n=3$; $n=1$ drop out) (11.3 vs. 354.0 kU/L; $^*P=0.0025$; Mann–Whitney test; Fig. 4). Serum peanut Ara h 2 IgE was also significantly reduced in the group who passed the 30-week challenge (Table 5). We also compared the pre-OIT challenge threshold, age at enrollment, presence of current asthma and rhinitis between these groups and found no difference (Table 5).

Table 5. Comparison of age at enrollment, total peanut serum IgE, Ara h 2 serum IgE, presence of current asthma or rhinitis and threshold dose before OIT between those who passed the 30-week peanut challenge ($n = 14$) and those who either reacted during the challenge ($n = 4$) or could not attempt it ($n = 1$ drop out; $n = 2$ unable to tolerate 800 mg OIT maintenance dose and $n = 1$ failed 6-week challenge)

	No reaction at 30-week challenge $n = 14$	Reaction at 30-week challenge $n = 8$	*P*-value
Pre-OIT challenge threshold (mg)	31 (1–110)	1 (1–81)	NS
Serum peanut IgE (kU/L)	6.44 (0.41–287)	354 (31.3–800)	0.0025*
Serum Ara h 2 (kU/L)	10.5 (0.35–⩾100)	⩾100 (29.1–⩾100)	0.0087*
Age (years)	12 (7–18)	9 (4–13)	NS
Current rhinitis	10 (71%)	4 (57%)	NS
Current asthma	6 (43%)	4 (57%)	NS

Figures are medians with ranges in parentheses unless otherwise stated.
*Mann–Whitney test for significance.
NS, non-significant; OIT, oral immunotherapy.

Discussion

In this study of 4–18 year-old peanut-allergic children, a gradual updose OIT regimen resulted in a 1000-fold increase in the amount of peanut tolerated, with an acceptable safety profile. All subjects tolerated a maintenance dose well above their pre-treatment challenge threshold, protecting against accidental ingestion.

This study has several novel features that distinguish it from the two studies recently published on this topic and provides valuable new information. We used a gradual updosing regimen, compared with previously published rush or semi-rush studies [14, 16]. We also used a higher top immunotherapy maintenance dose (800 mg compared with 300 mg [14] or 125 mg [16]). Also, in demonstrating desensitization we used a more rigorous final challenge with higher peanut dose than used in previous studies (6.6 g protein, compared with 2 g [16] or 3.9 g [14]), ensuring the detection of very high thresholds. We also identified that pre-OIT peanut-specific IgE may be a useful marker to stratify subjects into those who could be desensitized with relative ease and those who have greater difficulty. We performed threshold challenges before commencing immunotherapy and used these to guide the OIT starting dose [14]. Important new data on reactions due to extrinsic factors are described in the context of the overall safety data, which will inform future immunotherapy study design.

Our regimen was well tolerated by participants (Table 3). Two other groups have used more rapid updosing schedules, one had a 7-day rush protocol to a planned top dose of approximately 125 mg protein followed by a slower updosing for those who did not achieve this [16]. Seventy-four percent failed to increase their threshold during the rush period, but after gradual updosing 15/23 (65%) could tolerate 200–2000 mg of peanut. Overall 35% (8/23) dropped out. Jones et al. [14] used a 1-day rush to 50 mg of peanut protein with a planned top dose of 300 mg maintenance. Seventy-four percent failed to reach the intended top rush dose of 50 mg of peanut and 10% required adrenaline; overall 34% (10/29) withdrew from the study. Only 11/39 (28%) eventually passed a 3.9 g peanut challenge with no symptoms. In contrast, we found that 19/22 (86%) tolerated gradual updosing to 800 mg protein, with a good safety profile and only one withdrawal (Table 2). Fourteen of 22 (64%) passed a final 6.6 g peanut challenge with no reaction. A rush protocol has the advantage of reducing the number of updosing appointments but these studies suggest that such protocols are poorly tolerated and not particularly effective. Further study of rush protocols under anti-IgE cover is warranted.

We used a higher top maintenance dose than previous studies (800 mg protein vs. 300 mg [14] and 125 mg [16]), meaning that our subjects tolerated a greater amount of peanut and received a larger cumulative dose during immunotherapy. In subcutaneous immunotherapy, a higher immunotherapy dose is related to improved efficacy and this may help to explain the difference in outcome between studies. In our participants, OIT conferred protection against a minimum of 1.5 peanuts – much more than is likely to be encountered during accidental ingestion. For the majority, their tolerated dose was raised beyond 6.6 g of protein during challenge (14/22: 63%), a threshold higher than any previous study (3.9 and 2.0 g protein) [14, 16]. It was not known previously whether immunotherapy completely ablated reactivity, or simply raised the reactive threshold to a level somewhere above the immunotherapy dose. Using a lower cumulative challenge dose may not detect this increased threshold as 10–15% of peanut allergic subjects may still react to a higher dose [19].

This intervention would be most valuable to children with severe peanut allergy and/or low-dose thresholds. The study sample included children with typical peanut allergy, representative of most degrees of severity and threshold dose, with sensitization to the major peanut allergen (Ara h 2 – Table 2). Several children with a history of anaphylaxis were included. OIT with home dosing was well tolerated by the 14% with a history of

anaphylaxis and 8/22 with a very low threshold dose of 1 mg of peanut protein. Our data should provide reassurance for researchers considering whether to include such children in future studies. In our view, it is important that the treatment effect and safety be defined for children with high severity and/or low thresholds by larger studies.

The duration of OIT was shortened if the immunotherapy starting dose was high (subjects with higher dose thresholds were commenced on higher initial OIT doses) and lengthened if there was difficulty in updosing. The majority of participants tolerated the repeated planned dose increases and completed the protocol without major difficulty. A degree of flexibility in updosing is required because of differences in individual response to immunotherapy. Where reactions occurred on updosing, the dose was transiently reduced, but most continued to complete the protocol.

Limitations of the study were the lack of a control group and the small size. A control group would give further reassurance that the disease had not resolved spontaneously, even though this is unlikely given the short study duration. A small sample size was chosen because of the lack of published studies on this intervention. Nonetheless, sources of bias were offset by the powerful effect size observed.

It would be desirable to identify characteristics in advance of performing immunotherapy, which predict ease of desensitization or risk of reactions. Alternative strategies could then be used (e.g. more gradual dose increases). In this respect, the dose threshold was not helpful in predicting outcome. However, no subject with a peanut serum-specific IgE < 27.3 kU/L required alteration to their immunotherapy dose (8/8), so an IgE below this level may be associated with ease of immunotherapy. Further, subjects who failed or could not attempt the final peanut challenge had a significantly higher peanut-specific IgE than those who passed. These observations will be examined prospectively in a larger trial of peanut OIT.

An interesting and unexpected observation was that in the early stages of OIT, subjects often developed allergic reactions following ingestion of a previously tolerated dose, usually when an extrinsic factor was present. We have named these REFs. The 'extrinsic' factors were various, e.g. exercise within 2 h of a dose, excessive tiredness, exposure to an inhalant allergen known to cause respiratory symptoms (e.g. cat), infection and menstruation (in one subject). Asthma did not appear to relate to REFs but asthma was universally well controlled. Although some of these factors were present for all subjects at one time or another, this sensitivity was apparent in only 12/22 (54%). Such reactions could happen at any time during immunotherapy, but most occurred during the first few months (median time to last reaction was 3.7 months). Hence, it would seem that even though subjects are initially desensitized, they are still vulnerable and may react without warning when an extrinsic factor is applied. Although it was not observed, we are not excluding the possibility of loss of tolerance without an external factor. With continued immunotherapy beyond 6 months, this vulnerability reduces. We hypothesize that in the early stages of OIT, participants are partially desensitized and that the external factor lowers the reactive threshold to a level below the daily OIT dose, resulting in a clinical reaction. These reactions are well recognized in conventional subcutaneous injection immunotherapy, e.g. during an intercurrent infection. However, because OIT protocols require the allergen to be administered every day at home, there is concern that these reactions may occur when the patient is isolated from immediate medical assistance. We used this information to warn participants to avoid exercise after taking doses and if unwell to temporarily reduce the immunotherapy dose. Further study of the effect of extrinsic factors on tolerance of daily dosing is warranted. This finding also has relevance to reactions occurring 'in the field' in untreated patients. There is difficulty in predicting which peanut allergic patients are at risk of severe allergic reactions. It has been reported that some patients who have died of peanut anaphylaxis may have only had mild previous reactions [20]. While dose is a major influence on severity of individual 'field' reactions, extrinsic factors may also play a part.

It is likely that maintenance treatment will be required for at least 2–3 years, as for other forms of immunotherapy, before tolerance is achieved. It is not surprising that stopping peanut immunotherapy after a median of only 9 months resulted in loss of tolerance for 80% of subjects in the Blumchen study [16]. It may be possible to reduce OIT frequency when peanut serum-specific IgE levels have fallen to a low level but our study and others demonstrate that reduction in IgE takes years to occur [14, 16]. In addition, the ideal dose and frequency of 'occasional' peanut ingestion required to maintain tolerance to peanut need to be defined by long-term follow-up studies.

We recommend that peanut OIT should only be attempted as part of a clinical trial. There is a need to explore this intervention in large definitive trials. Results of larger randomized-controlled studies are required before this is accepted as a clinical treatment for peanut allergy.

In summary, using a new high-dose immunotherapy protocol with gradual dose increases we have shown that OIT is well tolerated and effective in typical peanut allergic patients, with improved outcome and acceptability. New information on updosing, use of peanut IgE to predict ease of desensitization and individualization of treatment for 'standard' and 'difficult to desensitize' patients has been provided. We have also revealed interesting safety data regarding reactions with extrinsic factors during immunotherapy. Overall, we have demonstrated

that it is possible to achieve an apparent 1000-fold increase in median-tolerated dose of peanut protein using OIT to treat children with peanut allergy.

Acknowledgements

We would like to thank the Evelyn Trust, Cambridge for providing financial support to Dr Anagnostou. We are grateful to the Cambridge Biomedical Research Campus and the Wellcome Trust Clinical Research Facility for hosting the research, the Golden Peanut Company, Alpharetta, GA, USA and Phadia AB, Uppsala, Sweden for providing materials and the Anaphylaxis Campaign, UK for help with publicizing the study. We are also grateful to Professor Wesley Burks (Duke University, NC, USA) for his advice.

References

1 Grundy J, Matthews S, Bateman B, Dean T, Arshad SH. Rising prevalence of allergy to peanut in children: data from 2 sequential cohorts. *J Allergy Clin Immunol* 2002; **110**:784–9.

2 Sicherer SH, Munoz-Furlong A, Sampson HA. Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. *J Allergy Clin Immunol* 2003; **112**:1203–7.

3 Kanny G, Moneret-Vautrin DA, Flabbee J, Beaudouin E, Morisset M, Thevenin F. Population study of food allergy in France. *J Allergy Clin Immunol* 2001; **108**:133–40.

4 Ho MH, Wong WH, Heine RG, Hosking CS, Hill DJ, Allen KJ. Early clinical predictors of remission of peanut allergy in children. *J Allergy Clin Immunol* 2008; **121**:731–6.

5 Primeau MN, Kagan R, Joseph L *et al*. The psychological burden of peanut allergy as perceived by adults with peanut allergy and the parents of peanut-allergic children. *Clin Exp Allergy* 2000; **30**:1135–43.

6 Avery NJ, King RM, Knight S, Hourihane JO. Assessment of quality of life in children with peanut allergy. *Ped Allergy Immunol* 2003; **14**:378–82.

7 Kapoor S, Roberts G, Bynoe Y, Gaughan M, Habibi P, Lack G. Influence of a multidisciplinary paediatric allergy clinic on parental knowledge and rate of subsequent allergic reactions. *Allergy* 2004; **59**:185–91.

8 Clark AT, Ewan PW. Good prognosis, clinical features and circumstances of peanut and tree nut reactions in children treated by a specialist allergy centre. *J Allergy Clin Immunol* 2008; **122**:286–9.

9 Ferdman RM, Church JA. Mixed-up nuts: identification of peanuts and tree nuts by children. *Ann Allergy Asthma Immunol* 2006; **97**:73–7.

10 Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. *J Allergy Clin Immunol* 1992; **90**:256–62.

11 Buchanan AD, Green TD, Jones SM *et al*. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007; **119**:199–205.

12 Longo G, Barbi E, Berti I *et al*. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J Allergy Clin Immunol* 2008; **121**:343–7.

13 Enrique E, Malek T, Pineda F *et al*. Sublingual immunotherapy for hazelnut food allergy: a follow-up study. *Ann Allergy Asthma Immunol* 2008; **100**:283–4.

14 Jones SM, Pons L, Roberts JL *et al*. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009; **124**: 292–300.

15 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**:286–91.

16 Blumchen K, Ulbricht H, Staden U *et al*. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010; **126**:83–91.

17 Clark AT, Islam S, King Y, Deighton J, Anagnostou K, Ewan PW. Successful oral tolerance induction in severe peanut allergy. *Allergy* 2009; **64**:1218–20.

18 Taylor SL, Hefle S, Bindslev-Jenson C *et al*. A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? *Clin Exp Allergy* 2004; **34**:689–95.

19 Taylor SL, Moneret-Vautrin DA, Crevel RW *et al*. Threshold dose for peanut: risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals. *Food Chem Toxicol* 2010; **48**:814–9.

20 Pumphrey RS, Gowland MH. Further fatal allergic reactions to food in the United Kingdom, 1999–2006. *J Allergy Clin Immunol* 2007; **119**:1018–9.