Study of induction of Tolerance to Oral Peanut: a randomised controlled trial of desensitisation using peanut oral immunotherapy in children (STOP II)

Katherine Anagnostou,[1] Sabita Islam,[1] Yvonne King,[2] Loraine Foley,[2] Laura Pasea,[3] Chris Palmer,[3] Simon Bond,[4] Pamela Ewan[1] and Andrew Clark[1]*

[1]Department of Medicine, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK
[2]Department of Allergy, Addenbrooke's Hospital, Cambridge, UK
[3]Centre for Applied Medical Statistics, Department of Public Health and Primary Care, University of Cambridge, Institute of Public Health, Cambridge, UK
[4]Cambridge Clinical Trials Unit, Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital, Cambridge, UK

*Corresponding author

Declared competing interests of authors: Andrew Clark and Pamela Ewan are inventors on a patent application covering the peanut protein dose range.

Published December 2014
DOI: 10.3310/eme01040

Scientific summary

Study of induction of Tolerance to Oral Peanut (STOP II)

Efficacy and Mechanism Evaluation 2014; Vol. 1: No. 4
DOI: 10.3310/eme01040

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Peanut allergy is a common and important medical condition, affecting 1% of children in developed countries, and rarely resolves. Peanut allergy is the most common cause of severe and fatal food allergic reactions and it is not possible to identify those at highest risk. The quality of life (QoL) of affected families is reduced because of constant fear over food choices and the likelihood of anaphylaxis. Despite the current best management, families of peanut-allergic children have poor knowledge of how to avoid and also treat food allergy emergencies. Accidental reactions are common (annual incidence rates for accidental reactions of up to 50% have been reported) and there is no disease-modifying treatment; therefore, the case is made for development of disease-modifying therapies. Oral immunotherapy (OIT) seems to be the most promising short- to medium-term solution to this problem, given its apparent efficacy in other allergies.

Grass pollen immunotherapy given by subcutaneous injection has been used for over a century to treat allergic rhinitis and has proven efficacy and safety. An early study of subcutaneous immunotherapy for peanut allergy showed a trend to benefit, but was terminated after severe adverse reactions. The oral route may be associated with increased safety and has been studied in cases of egg and milk allergy.

Subcutaneous peanut immunotherapy was first attempted in a small study in 1992, in which three subjects had a 67–100% reduction in symptoms induced by peanut challenge, suggesting that this is an effective therapy. No subject suffered anaphylaxis during immunotherapy. Sublingual immunotherapy for hazelnut allergy has been the subject of a more recent randomised controlled trial that showed significant increases in tolerance to hazelnut [assessed by double-blind, placebo-controlled food challenge (DBPCFC)] and systemic reactions were observed in only 0.2%. We chose to use the oral route as we expect this to induce fewer side effects than injection immunotherapy, while still being efficacious, as demonstrated for pollen immunotherapy. There are preliminary studies on desensitisation to other food allergens such as milk and egg.

We have pilot data on children aged 5–18 years, using a study design identical to that of the active arm in the proposed trial. All had peanut allergy confirmed by blinded challenge before progressing to OIT according to the current proposal. To date, 19 out of 22 children have reached the final dose of 800 mg of peanut protein and are taking this, the equivalent of five peanuts, at home with no reaction. OIT doses taken at home and on the research ward are well tolerated and no subject has had a severe or generalised reaction during up-dosing. There is a need for systematic study of peanut OIT.

Objectives

We previously performed a phase 1 study that showed good tolerability and an indication of good efficacy. The current study is a phase 2 randomised controlled study of the efficacy of peanut OIT in achieving desensitisation in a well-characterised population.

Method

The overarching objective was to determine efficacy of OIT in desensitising children with peanut allergy. We aimed to determine whether or not the treatment was successful in the intervention group compared with the control (phase 1), and whether or not it is successful when offered to the control group (phase 2).

Eligible patients were aged between 7 and 15 years of age, of either sex, with peanut allergy confirmed by a clinical history of a typical rapid-onset immediate-type hypersensitivity reaction after peanut ingestion, positive skin prick test (SPT) to peanut (extract from ALK-Abelló; Hørsholm, Denmark) defined by a weal of ≥ 3 mm in the presence of a negative control and positive histamine control, and positive DBPCFC. We excluded patients if they had a clinically apparent immunodeficiency, but we did not exclude patients who had a previous reaction that was severe, or life-threatening.

Subjects were randomised in a 1 : 1 ratio via a central audited online response system to an active or control group. During phase 1, the active group underwent 6 months of active OIT and the control group underwent 6 months of standard care (peanut avoidance). At the end of phase 1 (6 months), all participants were assessed for peanut allergy by DBPCFC. During phase 2, participants in the control group still allergic to peanut after 6 months of standard care were given active OIT, followed by a DBPCFC after 6 further months.

The primary outcome of 'no reaction' during a DBPCFC was assessed using an objective, blinded measure. The primary end point was the proportion of desensitised subjects at the end of phase 1. Desensitisation was defined as 'no reaction' during peanut DBPCFC with a cumulative dose of 1400 mg of peanut protein.

The secondary end points were:

- proportion who responded to treatment after receiving OIT (a response to treatment was defined as ingesting 800 mg of peanut protein regularly for up to 6 months)
- proportion of the control group who were desensitised or responded to treatment during phase 2
- fold and absolute increase in threshold [maximum tolerated peanut protein (mg)] after OIT
- change in QoL scores [measured by food allergy quality-of-life questionnaire – parent form (FAQLQ-PF) 0–12 years] from baseline to the end of phase 1 and phase 2
- adverse events
- immunological outcomes [basophil area under curve (AUC) percentage of CD63 and mean fluorescent intensity (MFI), peanut immunoglobulin E (IgE), total IgE and SPT diameter].

Oral immunotherapy

The active intervention (OIT) was administered in daily doses throughout and was given in two phases. First, there was a gradual up-dosing phase with 2-weekly increments to 800 mg/day, followed by a maintenance phase in which the highest tolerated dose (with a target of 800 mg/day) was taken continuously to complete a total of 6 months' immunotherapy. The same characterised peanut flour used in the challenges was also used for up-dosing (light roast flour; Golden Peanut Company, LLC, Alpharetta, GA, USA). The same dose was administered at home daily for 2–3 weeks.

Flow cytometric analysis (fluorescence-activated cell sorting) of patient samples was undertaken on whole-blood specimens by study staff to quantify the percentage and MFI of CD63+ basophils. SPTs were undertaken using a standardised peanut extract from ALK-Abelló (Hørsholm, Denmark) and a single-point lancet. Peanut-specific serum IgE was measured using the ImmunoCAP system (Thermo Scientific, Hørsholm, Denmark).

Statistical analysis

Fisher's exact test was used to compare the proportion of those with desensitisation to peanut after 6 months in the active group with the control group at the end of phase 1. Multiple logistic regression

was used to adjust the odds of desensitisation for baseline characteristics. Secondary analyses tested for treatment differences with Fisher's exact test (proportion response to treatment in active group and control group at end of phase 2), paired and independent sample *t*-tests (absolute and fold change in threshold) and Mann–Whitney *U*-tests (change in QoL scores, basophil AUC of percentage of CD63 and MFI, peanut-specific serum IgE and SPT weal diameter). All statistical tests described in this section use a two-sided 5% significance level. We performed analysis on the intention-to-treat population that included all those who were randomised and participated in at least one post-baseline assessment.

Sample size was based on Fisher's exact test with 90% power and 5% significance (two-sided). A sample size of 49 in each group is sufficient to detect proportions of participants with desensitisation to peanut of 0.64 and 0.30 in the active and control groups, respectively, at the end of phase 1. Allowing for 5% dropout increased the required sample size to 52 participants in each group and 104 subjects overall. Based on the above, we would expect 35 waiting list group patients to proceed to the active intervention in phase 2. Non-parametric tests may be used instead of parametric tests if the assumptions are not appropriate.

Results

We enrolled 104 children, aged 7–16 years (median 12.4 years), to the study. Five children did not react during their baseline peanut challenge, thus not meeting the inclusion criteria, and were excluded from further participation in the study. Therefore, 99 out of 104 children were randomised: 49 out of 99 to the active group and 50 out of 99 to the control group. One child was discontinued and five withdrew from the active group during phase 1. In the control group, four children withdrew and one was discontinued during phase 1. Two further children withdrew from the control group when they underwent the intervention in phase 2.

Primary objective

There was a significant difference between the numbers of patients who tolerated 1400 mg of peanut protein during DBPCFC at the end of phase 1 in the active (24/39) compared with the control group (who underwent peanut avoidance for 24 weeks) (0/41) ($p < 0.001$). The proportions desensitised during phase 1 after 24 weeks were 0.62 (range 0.45–0.78) and 0 (range 0–0.091) in the active and control groups, respectively.

Secondary objectives

Response to treatment, defined by the ability to tolerate daily doses of 800 mg of peanut protein after 24 weeks of immunotherapy, occurred in 0.84 [95% confidence interval (CI) 0.70 to 0.93] of the active group at the end of phase 1 and 0.91 (95% CI 0.79 to 0.98) of the control group at the end of phase 2 (post immunotherapy). There was a significant increase in peanut no observed adverse effect level (NOAEL) in the active group after phase 1, with a median change in threshold of 25.5-fold ($p < 0.001$) compared with a small positive change in peanut threshold (NOAEL) in the control group during phase 1 (0.80, range 0.05–1.82).

The proportion of patients who achieved desensitisation (0.54, 95% CI 0.35 to 0.72) or response to treatment (0.91, 95% CI 0.79 to 0.98) in the control group after 24 weeks of OIT (end of phase 2) was similar to that in the active group [0.62 (range 0.45–0.78) and 0.84 (95% CI 0.70 to 0.93), respectively].

Quality-of-life end points

Quality-of-life scores assessed by the FAQLQ-PF measure were similar between active and control groups at baseline (2.28 vs. 3.61). After treatment in both groups there was a similar and clinically meaningful improvement (decrease) in QoL scores (control –1.41, 95% CI –4.83 to 1.38; active –1.61, 95% CI –4.87 to 0.24; $p < 0.001$).

Immunological assessments revealed a significant small reduction in median SPT weal diameter (–1 mm, range –8 to 4 mm; $p = 0.0015$) and an increase in peanut-specific serum IgE (12.7 kilounit (kU)/l, range –18.6 to 1359 kU/l; $p < 0.001$) after 24 weeks' OIT in the active group. Basophil stimulation tests data were expressed as the AUC of plots of MFI and percentage of CD63-positive cells against concentration of peanut protein. No significant within-patient differences were found after treatment for AUC of MFI or percentage of CD63-positive cells although there was a reduction in MFI and percentage of CD63-positive cells at the lower peanut doses.

Logistic regression revealed that several baseline covariates had an influence on the final NOAEL (the highest amount of peanut tolerated after OIT). Treatment, log-baseline NOAEL, age, family history and log-transformed peanut-specific IgE have a statistically significant effect on log-transformed NOAEL at 6 months. On average, patients in the OIT group have a log-NOAEL at 6 months 4.12-fold higher than those in the waiting list group. For every unit increase in log-transformed baseline NOAEL, the log-transformed NOAEL at 6 months, on average, increases 0.33-fold. For every year increase in age at baseline, the log-transformed NOAEL at 6 months decreases, on average, by 0.17. Patients with a family history of peanut allergy have, on average, 0.64 lower log-transformed NOAEL at 6 months than patients who do not have a family history of peanut allergy.

The number of adverse events was similar in both groups after treatment. The majority of events were gastrointestinal, with oral itching being most common (occurring after 6.3% of all doses); cutaneous events were uncommon, appearing after only 0.16% of doses. Wheezing occurred after 0.41% of doses and was treated with inhaled beta-2 agonists or oral antihistamines in all cases except for one participant who also received intramuscular epinephrine on two occasions, with rapid resolution of his symptoms. There were no serious adverse reactions and no cardiovascular events.

Conclusions

In children aged 7–15 years with challenge-proven peanut allergy of any severity, peanut OIT successfully induced desensitisation in the majority with a clinically meaningful increase in peanut threshold. There was a high rate of response to treatment in both the active and control groups, after undergoing OIT. Immunological changes reflected clinical desensitisation. QoL improved after intervention and the safety profile was acceptable. Peanut OIT offers a highly efficacious treatment for peanut allergy in children.

Peanut allergy is a highly homogeneous disease, with well-validated diagnostic tests and minimal variation in phenotypic characteristics. Future confirmatory trials are desirable, but given the highly homogeneous nature of the illness and the strong effect size observed in this study, such trials are unlikely to require large numbers of patients.

This study provides a protocol for the study of OIT to other allergens that commonly cause food allergic reactions in adults and children. These include tree nuts, milk, egg, fish and shellfish. Similar studies of OIT using these allergens are required to demonstrate whether or not this treatment regime can be translated to treat other common and potentially severe food allergies.

Trial registration

This trial is registered as ISRCTN62416244.

Funding

This project was awarded by the Efficacy and Mechanism Evaluation programme and is funded by the Medical Research Council (MRC) and managed by the National Institute for Health Research (NIHR) on behalf of the MRC–NIHR partnership, and jointly sponsored by the University of Cambridge and Addenbrooke's Hospital [Cambridge University Hospital Foundation Trust (RD authorisation A091686)].

Efficacy and Mechanism Evaluation

ISSN 2050-4365 (Print)

ISSN 2050-4373 (Online)

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: nihredit@southampton.ac.uk

The full EME archive is freely available to view online at www.journalslibrary.nihr.ac.uk/eme. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Efficacy and Mechanism Evaluation* journal

Reports are published in *Efficacy and Mechanism Evaluation* (EME) if (1) they have resulted from work for the EME programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

EME programme

The Efficacy and Mechanism Evaluation (EME) programme was set up in 2008 as part of the National Institute for Health Research (NIHR) and the Medical Research Council (MRC) coordinated strategy for clinical trials. The EME programme is broadly aimed at supporting 'science driven' studies with an expectation of substantial health gain and aims to support excellent clinical science with an ultimate view to improving health or patient care.

Its remit includes evaluations of new treatments, including therapeutics (small molecule and biologic), psychological interventions, public health, diagnostics and medical devices. Treatments or interventions intended to prevent disease are also included.

The EME programme supports laboratory based or similar studies that are embedded within the main study if relevant to the remit of the EME programme. Studies that use validated surrogate markers as indicators of health outcome are also considered.

For more information about the EME programme please visit the website: http://www.nets.nihr.ac.uk/programmes/eme

This report

The research reported in this issue of the journal was funded by the EME programme as project number 08/99/18. The contractual start date was in January 2010. The final report began editorial review in July 2013 and was accepted for publication in April 2014. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The EME editors and production house have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the final report document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research. The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, MRC, NETSCC, the EME programme or the Department of Health. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the EME programme or the Department of Health.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).