Project Description

Title

Full Title:
Optimizing treatment adherence and supporting ongoing desensitization following peanut oral immunotherapy in children: a randomized controlled trial of daily versus weekly peanut ingestion

Short Title:
Optimizing post-desensitisation adherence

Acronym:
Post-HYPES (post-HYpoallergenic Peanuts Eaten Safely)

Version Number:
Version 2

Project Team Roles & Responsibilities

Dr Billy Tao
Dr Scott Morris
Dr Sarah Cohen-Woods
Dr Luke Grzeskowiak
Dr Tim Chataway

Resources

1. Roasted peanuts for the trial are provided by the Flinders Proteomics Facility at Flinders Medical Centre, with full quality control and standardized production procedures.
2. Participants will be interviewed at Allergy SA
3. The questionnaires used in this study are provided by CI Dr Sarah Cohen-Woods following appropriate copyright applications / payments.
4. An Honours Psychology student will be involved in assisting the administration and analysis of the questionnaires, under supervision of Dr Cohen-Woods.
5. Funding was provided by a Channel 7 Children's Research Foundation grant of $74,843.

Background and Rationale

An overview of our current peanut research
Peanut oral immunotherapy (POIT) is the most studied method for peanut desensitisation [1-11]. However, a major problem with POIT is the high rate of adverse events during

treatment, necessitating frequent hospital visits and causing drop-outs. To illustrate this, in the study of Tang et al. involving probiotics and peanut (PPOIT) [8], of the 31 children randomised to immunotherapy (from n=62), 10% withdrew, 45.2% had at least 1 severe AE (one subject had 13 severe AEs) and 7 subjects reported a total of 10 serious adverse events (SAEs). Treatment usually began with one full day of repeated small-dose escalations followed by biweekly up-dosing for another 8 months, all done in hospitals. Such frequent visits are inconvenient, expensive and burdensome to both patients and service providers.

In 2017 our group published a pilot study of 14 peanut allergic children utilizing a sequential (biphasic) OIT protocol involving firstly 2-hour boiled, and then roasted peanuts [12], funded by Channel 7 CRF. Two withdrew (unrelated to any AE) but the remaining 12 subjects all tolerated 8-10 roasted peanuts at end of desensitisation. Three subjects (25%) reported mild AE in the early stages of boiled peanut desensitisation while two (17%) experienced similarly mild AE in the first week of roasted peanut desensitisation. The study established the feasibility of our sequential boiled-to-roasted peanut OIT as a uniquely cost-effective, low-risk and efficacious technique undertaken in an entirely outpatient environment. This has major implications for peanut desensitisation as it opens the door to treating large number of affected patients in friendly surroundings with minimal intrusion and general affordability.

In 2017/18 we received our second Channel 7 CRF grant to complete a Phase 2 clinical trial on peanut-allergic children, using an improved version of the previously piloted biphasic boiled-to-roasted OIT protocol, again in a non-hospital-based setting. The new trial differs from the pilot study in that: (a) it includes many cases of severe peanut allergy, (b) it is a 3-step procedure starting with 12-hour boiled peanut, then 2-hour boiled and finally roasted peanut, while the pilot study used a 2-step procedure starting with 2-hour boiled and then roasted peanut, (c) the commencing dose in each phase is $1/16^{th}$ of a peanut instead of 1/4, further reducing the risk of AE, and (d) doses are administered twice daily instead of three times daily at home, making it more convenient for parents. Enrolment began in mid-2017 and is due for completion in mid-2019. Of the 69 children currently enrolled, there have been only mild AEs, mainly oral symptoms at ingestion and skin rashes which were often triggered by unplanned or unintentional physical exertions. This study when completed will have immediate and significant applications in community-based medical care.

While these promising results may well address the critical limitations of other peanut OIT methods, an important point to emphasise is that desensitisation actually accounts for only the first year of treatment, after which regular maintenance of peanut ingestion demands much longer patience and perseverance. This is of great importance because many children dislike the taste of peanut and can be distressed by the association between taste and past allergic experience. Furthermore, having developed a lifestyle of avoidance, this may actually be considered preferable to daily ingestion of peanuts. It is therefore timely to shift focus from initial safety to ongoing adherence.

Poor treatment adherence in ongoing maintenance therapy

The proportion of peanut-desensitised children dropping out from regular ingestion is not clear, but known to be high. In a recent long-term follow-up study of peanut sublingual immunotherapy involving 40 subjects aged 12-40 [13], 37 achieved desensitisation but 23 (62%) had chosen to discontinue treatment within 3 years. In the follow-up study of

PPOIT by Hsiao et al. (published on line, Lancet Child Adolescent Health, 2017 1:97-105), of the 24 children reviewed 4 years after initial desensitisation (original n=31), 8/24 (33%) had discontinued eating peanuts by choice while the fate of the other 7 (n=31-24) was unknown. In our own experience with the pilot study, 11 treated patients were contacted by telephone approximately one year after completion (one of the original 12 could not be contacted), and only 5 of them (45%) were still eating peanuts regularly, despite being told to continue eating after desensitisation. This indicates a drop-out rate in excess of 50% over time, which needs to be improved.

Limitations of current literature

A major design-limitation of all currently published OIT studies is that they do not incorporate a well-structured protocol for maintenance therapy post-desensitisation. This may contribute to non-adherence. A well-designed and high-quality post-desensitisation study is therefore urgently needed to make best use of the time and expense already put into OIT while maintaining long-term benefit of desensitisation in the years that follow.

Psychological considerations and quality of life

There is a large body of evidence highlighting the impact of peanut allergy on the quality of life (QoL) of affected children and their families. Constant vigilance is needed to avoid allergens and the daily management of food allergy directly affects family activities and social events. Bollinger et al. [14] investigated the care-giver's perspective of the impact of a child's food allergy on different aspects of life, including daily social events, field trips, parties, sleepovers and playing at friends' houses. One-half of families reported significant disruption to their lives. Many parents would rather minimise the risk or anxiety induced by such activities simply by avoiding them altogether or accompanying their children in social situations beyond the age at which non-allergic children are generally accompanied. Many parents dread taking their children to eat away from home and, when they do, prefer to take them to the same restaurants that they have tried before and who they know look after their allergic clients. Peanut allergy has also forced parents and siblings to share the same restriction put in place because of their relationship with the child, so food limitations are imposed on all family members. Avery et al. [15] found that children with peanut allergy reported lower quality of life scores than children with insulin-dependent diabetes mellitus (IDDM) and were more afraid of accidentally eating peanuts than children with IDDM were afraid of having a hypoglycaemic event.

Successful desensitisation can reduce such anxieties by offering the child protection from accidental ingestion of at least the same amount of desensitisation-dose peanut. Dunn Galvin et al. recently compared QoL of desensitised (n=24) vs placebo-treated (n=27) groups and found sustained psychological benefit only in treated subjects at 3- and 12-months after end-of-treatment [16]. However, no such studies have been done to compare QoL between adherent and non-adherent subjects post-desensitisation. The fact that many desensitised children have opted to drop-out from treatment rather than maintaining ingestion is concerning, while it may also indicate that the time immediately after desensitisation could in fact be an inflexion point for QoL changes. We think this study will reveal vital data in the understanding of causes and consequences of longer-term poor adherence after initially successful desensitisation.

Immunological changes over 12-months post-desensitisation

It is well known that during desensitisation (peanut-specific) psIgE falls and psIgG4 rises, and that psIgG4 can block mast cell activation by psIgE in the presence of peanut antigen

[17]. However, it is not known if the elevated level of psIgG4 is maintained throughout the post-desensitisation period.

Justification of the maintenance dosage

In comparing daily versus weekly regimens in our research plan we have chosen 2 jumbo peanuts (each weighing 1gm equivalent to 250mg peanut protein) as the daily maintenance dose and 14 peanuts as weekly dose. The rationale for choosing 2 peanuts as daily maintenance is based on a recent OIT study in Japan [10]. Traditionally a maintenance dose is lower than an eliciting dose at OFC, and in this Japanese study 24 subjects with peanut allergy were initially hospitalised for 5 days and given increasing amounts of peanut powder up to 133mg/day (about ½ peanut) by the last day of hospitalisation. This same small dose was maintained for a full year without further increment, and subjects then underwent OFC after avoiding peanuts for 2 post-maintenance weeks. The challenge dose was set at 795mg (about 3 peanuts or 6 times higher than the maintenance dose). Eight (33%) subjects passed the OFC.

A vision for the future

Our bold vision for this project is to develop a comprehensive package for the care of peanut-allergic children in a clinical centre of excellence, building on our boiled-to-roasted peanut OIT technology with a sound evidence-based maintenance program, thereby extending the long-term benefit of desensitisation with improved adherence, safety and quality of life. Our group already has expertise in the manufacture and quality-control of boiled peanut at Flinders Medical Centre Proteomics Facility, and we have also been making progress in scientific research in immunologic aspects of peanut and other nut allergies. Our desensitisation method is unique among others in being performed entirely outside hospitals, and thus allows large numbers of patients to be treated efficiently and safely in the community. Currently an evidence-based post-desensitisation protocol does not even exist at any other institution in the world, and the completion of this proposal would certainly facilitate translation to practice of a greatly improved long-term therapy for peanut allergy, benefiting many children and their families.

Research Questions and Aims

Peanut allergy affects up to 3% of Australian children and in most cases is a life-long condition. Desensitisation, while not a cure, is the only proactive and disease-modifying therapeutic approach currently available. Oral immunotherapy (OIT) is the most effective desensitisation method but is hampered by high rates (45-93%) of adverse events (AEs). Preliminary data from 69 children currently participating in our Phase 2 clinical trial of sequential boiled-to-roasted peanut OIT, funded by Channel 7 Children's Research Foundation in 2017-18, suggest that our unique OIT method is effective and has a low AE rate.

However, desensitisation using OIT can only confer temporary protection and requires ongoing peanut maintenance consumption, typically for many years or even life-time. Limited published data available have indicated that adherence to maintenance peanut consumption is poor, but the dearth of good studies has been a major limitation in the evaluation of long-term utility of existing randomised controlled trial evidence. Also, current data have provided no insight on the reasons for, or solutions to, the important problem of non-adherence.

With impending completion of our Phase 2 clinical trial on peanut oral immunotherapy in early 2019, we are well-positioned to investigate if we can observe improved adherence to peanut consumption in any one of the two different regimens and arrive at possible reasons for non-adherence. Through randomisation we aim to determine whether allocating children to either daily or weekly peanut ingestion as post-desensitisation maintenance is associated with measurable differences with respect to:

- Ongoing peanut desensitisation as determined by oral food challenges
- Immunological changes as indicated by serial skin prick tests, serum levels of peanut-specific IgE and IgG4, and mast cell activation tests
- Treatment adherence and continuation of peanut ingestion for 12-months;
- Quality of Life, treatment satisfaction and adverse events.

Hypothesis and Expected Outcomes

No studies have previously investigated different approaches for ongoing maintenance of peanut ingestion after initial success in oral immunotherapy. Poor treatment adherence post-desensitisation is a major issue, with available literature demonstrating more than 50% of treated children stop eating peanuts within 2-3 years after desensitisation. This places them at renewed risk of anaphylaxis as they are no longer desensitised to peanuts, and also represents a significant waste of resources involved in earlier treatment effort.

We hypothesise that (after randomising post-desensitisation subjects into two different schedules - one ingesting peanuts daily and the other weekly):

1. Children who continue to ingest peanuts either weekly or daily will maintain their peanut-desensitised status at 12-months as evaluated through oral food challenges consisting of 12 peanuts.
2. Weekly or daily ingestion will demonstrate similar profiles of tolerability and adverse events.
3. The two groups will also demonstrate similar immunological profiles in terms of skin prick tests, serum peanut-specific IgE and IgG4 levels.
4. However children randomised to weekly peanut ingestion will have better adherence at 12 months compared to those randomised to daily ingestion.
5. Non-adherence to treatment protocol or withdrawal will be associated with poorer psychological measures and quality of life

References

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Project Design

Methodological Approach:
The design will be a Randomised Controlled Trial with 3 study visits - at baseline, 6 months and 12 months respectively. There will also be 2 phone calls at 3 months and 9 months.

Participants:
All children successfully desensitised in Phase-II clinical will be invited to participate in this project. Subjects who had failed to be desensitised, or had withdrawn from the previous trial, will not be eligible for this randomised study. Based on feedback from research assistant (RA) of the previous trial we expect at least 60 interested participants.

Invitation to participate and collection of signed consent (PICF):
The Research Assistant (RA), who was involved in the HYPES study and therefore knew very well the children and their family members from the old study, will contact potential participants of this new study by phone, and invite them to participate again. A telephone script for the recruitment has been drafted, and the document will be uploaded for ethics approval.

After the telephone invitation, if parents of children showed interest in the new trial, an appointment will be made for the RA to meet the respondents, at Allergy SA. To avoid conflict of interest, Dr Tao will not be present at the meeting, which will take about an hour to allow adequate time for explanation.

The parents/caregivers will take the PICF home to study, and discuss among family members, friends and third party individuals such as their family doctors, and this will include the children themselves. A follow-up phone call from the RA will be made within 2 weeks.

A separate consent will be obtained from parents/caregivers and older participating children if they want to be involved in the decision making.

Randomisation:
Treatment will be assigned with the help of a computer-generated randomisation schedule (using www.randomization.com), with treatment assignment concealed in opaque envelopes. Due to the nature of the study it will not be possible to blind the clinician, parents/carers or child to treatment allocation. Randomisation will be into one of the two treatment schedules, stratified by whether the child likes or dislikes eating peanuts.

Treatment Schedules:
There will be two randomised groups:

A. **Daily:** Children ingesting at least 2 peanuts daily.
B. **Weekly:** Children ingesting at least 14 peanuts on one day once a week.

In both groups, children will be allowed to consume ad libitum additional peanuts or peanut protein in other food such as peanut butter/paste.

Treatment Supply:

All roasted peanuts for maintenance will be supplied by Flinders Proteomics Facility to participants, free of charge and in individually labelled containers. The Facility will also provide full quality control of peanuts.

Study Outcomes:

1. **Primary outcome:** Ongoing desensitisation to peanut as determined by successful completion of oral food challenge.

2. **Secondary outcomes:**
   - Adverse events.
   - Immunological changes in terms of serial skin Prick Tests, peanut-specific IgE and IgG4 levels. We are particularly interested to see if recurrent high-peak (weekly 14-peanuts) versus steady low-dose (daily 2 peanuts) can lead to different IgG4 levels.
   - Parental questionnaires: Food Quality of Life; Depression, Anxiety and Stress Scale, Perceived Stress Scale; Food Allergy Quality of Life Burden Scale
   - Child Questionnaires: Peanut Allergy Quality of Life; Revised Children's Anxiety and Depression Scale; Perceived Stress Scale for Children

Study Withdrawal:

Patients and children in either group can elect to stop eating peanuts altogether at any time during study and withdraw. Parents and children can elect to withdraw completely, or from just the questionnaires, and/or blood and skin prick tests. If they do they will be provided the opportunity to complete an exit questionnaire designed to understand why they have chosen to stop ingestion.

Ongoing Monitoring:

- Children and their parents will be interviewed face-to-face at baseline, 6 months and 12 months, when skin prick tests will be performed, blood samples taken for psIgE and psIgG4, mast cell activation tests, and questionnaires administered at Allergy SA.
- In addition, there will be two telephone calls to participants by the research assistant (RA) mainly for safety monitoring at 3 months and 9 months.
- Parents will also have the opportunity to contact RA any time if there is an adverse event, question, or change of mind in treatment continuation.

Otherwise, no further contact will be made to participants in order to ensure minimal interference with treatment adherence over the 12-month maintenance period.

Special Transition for Group B Participants - from Daily to Weekly Ingestion:

1. Immediately after enrolment, subjects in Group B will increase their daily ingestion of peanuts from 12 per day to 14 per day over a 2 week period. They will then enter a transition phase, taking approximately 3 months to achieve:
2. Ingest peanuts every second day: on Day 1, 3, 5.
3. Ingest every third day: on Day 8, 11, 14.
4. Ingest every fourth day, on Day 18, 22, 26.
5. Ingest every fifth day, on Day 31, 36, 41.
6. Ingest every 6^{th} day, on Day 47, 53, 59.
7. From Day 66 onwards: ingest once a week for the remaining treatment period of 12 months.
8. Patients are assessed at 3 months to see if the transition is successful.

9. An interim peanut challenge will be arranged at Allergy SA, after participants from this group have successfully transitioned from eating daily to eating weekly, within that 3-month period. This will be done before commencement of the next 9 months of weekly ingestion of roasted peanuts, to make sure that next phase of the study for this group of participants is safe.

Oral Food Challenges:

All oral food challenges will be undertaken at Allergy SA under direct supervision of the chief Investigator (BT), who is an experienced specialist allergist, and has performed such challenges regularly at his private practice, including those for the previous HYPES study, which had received full ethics approval. The site is fully equipped to deal with any anaphylactic emergency reaction during a challenge. Because participants were already eating 12 peanuts in one setting at the end of previous desensitisation study, this will also be the challenge dose for this study. All participants will be observed for 2 hours after the last dose of challenge. There will be 3 types of oral food challenges:

1. **Interim food challenge at completion of transition for Group B (Weekly) participants:**
   - Before arrangements are made for the challenge, the RA will contact participants in Group B (weekly) to make sure that they are already eating 14 peanuts every day at home. The actual food challenge procedure is the same as the final OFC for Group B as detailed below

2. **Special OFC schedule for Group A (daily) participants (in 3 days for increased safety):**
   - On day 1: At Allergy SA, subjects will ingest 2 peanuts soon after arrival, wait for ½ hour, then another 2 peanuts, wait for another ½ hour and, if no adverse reaction, ingest the last 2 peanuts, making a total of 6 peanuts cumulatively on Day 1. Subjects will be observed for two hour before discharge.
   - On day 2: After arrival, subjects will ingest a single dose of 6 peanuts, wait for ½ hour, then 2 more peanuts, wait for another ½ hour, then another 2 peanuts, wait for another ½ hour, then finally the last 2 peanuts, making a total of 12 peanuts cumulatively on Day 2. Subjects will be observed for two hour before discharge.
   - On day 3: subjects will be witnessed to ingest 12 peanuts as a single dose, and then observed for two hour before discharge. Success at OFC indicates that the participants have maintained their protection 12 months after desensitisation.

3. **OFC for Group B (weekly) participants:**
   - Subjects will be witnessed to ingest 12 peanuts as a single dose at Allergy SA, thus confirming that they have maintained their protection 12 months after desensitisation.

The decision to proceed with the final OFC is made, and then arranged, at the last visit of the 12-month study period. A prerequisite for OFC is that participants must be fully-adherent to the protocol in the preceding 2 weeks. For the weekly group (Group B) they will simply return at the next scheduled ingestion date and be witnessed eating 12 peanuts at Allergy SA. For the daily group (Group A), it will be a 3-day event as explained above.

Psychological Measures and Questionnaires:

Questionnaires will be administered to measure quality of life, depression and anxiety, as well as stress factors among children and parents throughout study. These questionnaires have all been well-validated in their target population of children or parents, and will be administered to both groups.

We intend to investigate the relationship between psychological measures and treatment adherence and satisfaction. The depression, anxiety, and stress measures will be used to investigate any relationship with adherence and quality of life.

The questionnaires will be printed in hard copies and administered to parents at Baseline, 6-months and 12-months respectively at Allergy SA, at the same interview when skin tests are also performed and blood samples taken. Some questionnaires will be completed at the site but the remaining unanswered questions will be allowed to take home and be answered at a more leisurely pace. Parents will be given a pre-addressed and reply-paid envelope to send the answers back to the RA, who will check with parents if she has not received the envelope after 2 weeks.

The following are the lists of questionnaires:

Children:

- **Quality of life -** Peanut allergy PedQL (Pediatr Allergy Immunol 2003;14:378);
- **Depression and anxiety scores -** Revised Children's Anxiety and Depression Scale (RCADS), (https://www.corc.uk.net/outcome-experience-measures/revised-childrens-anxiety-and-depression-scale-and-subscales/)
- **Stress -** Perceived Stress Scale for children (PSSC), (https://www.researchgate.net/publication/277630701_The_Perceived_Stress_Scale_for_Children_A_Pilot_Study_in_a_Sample_of_153_Children).

Parents:

- **Quality of life** -
  - Food Quality of Life Questionnaire Parent Form (DunnGalvin et al 2008)
  - Food Allergy Quality of Life Parental Burden Scale (Cohen et al 2004)
- **Depression and anxiety scores** - Depression, Anxiety, and Stress Scale (DASS) (Lovibond & Lovibond, 1995).
- **Stress** – perceived stress scale (PSS).

Sample Size and Statistical Analysis:

- Analysis will be undertaken according to intention-to-treat principle.
- Dichotomous outcomes, including successful completion of oral food challenges, proportion experiencing adverse effects, and adequate treatment adherence, will be assessed by calculating a risk ratio (RR) with 95% CI, determined with a log-binomial model.
- Food related QOL at end of trial will be compared between groups using linear-mixed models, adjusting for food related QOL.
- Appropriate statistical analyses for immunological parameters will be undertaken according to underlying distribution of each variable (i.e. IgE, IgG4, skin pricks). Differences between groups at baseline, 6 months and 12 months will be compared using *Two Sample t-Test* or *Wilcoxon Rank Sum Test* for parametric and non-parametric data respectively. Differences within group across time will be compared

using *Paired t-Test* or *Wilcoxon Signed Ranks Test* for parametric and non-parametric data respectively.

- A p-value of less than 0.05 will be considered to indicate statistical significance.

Power calculation:

The overall sample size is capped according to the number of children who have complete the original HYPES study. HYPES enrolled 69 children and we estimate that 60 of these would consist to this post-HYPES study. While the sample is small, this study will provide critical data to inform the development of larger clinical trials and demonstrate the feasibility of evaluating outcomes associated with ongoing maintenance regimens following successful peanut desensitisation. Based on the limited number of eligible children, a total of 60 participants (30 in each group) would provide 80% power (alpha 0.05) to detect an absolute difference of 25% with respect to successful completion of OFC or non-adherence/withdrawal from treatment. Previous literature and our own clinical experience indicates that non-adherence to peanuts is a major problem, with 33-62% of children becoming non-adherent within 12-36 months of successful peanut desensitisation. Therefore our study is sufficiently powered to determine whether frequency of peanut ingestion is associated with a 25% or greater difference with respect to treatment adherence.

Flow Chart