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Peanut Allergen Threshold Study (PATS): Novel Single-Dose Oral Food Challenge Study to Validate Eliciting Doses in Children with Peanut Allergy

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Abstract

Background: Eliciting doses (EDs) of allergenic foods can be defined by the distribution of threshold doses for subjects within a specific population. The ED_{05} is the dose that elicits a reaction in 5% of allergic subjects. The predicted ED_{05} for peanut is 1.5 mg of peanut protein (6 mg of whole peanut). *Objective:* We sought to validate the predicted peanut ED_{05} (1.5 mg) with a novel single-dose challenge. *Methods:* Consecutive eligible children with peanut allergy in 3 centers were prospectively invited to participate, irrespective of previous reaction severity. Predetermined criteria for objective reactions were used to identify ED_{05} single-dose reactors. *Results:* Five hundred eighteen children (mean age, 6.8 years) were eligible. No significant demographic or clinical differences were identified between 381 (74%) participants and 137 (26%) nonparticipants or between subjects recruited at each center. Three hundred seventy-eight children (206 male) completed the study. Almost half the group reported ignoring precautionary allergen labeling. Two hundred forty-five (65%) children experienced no reaction to the single dose of peanut. Sixty-seven (18%) children reported a subjective reaction without objective findings. Fifty-eight (15%) children experienced signs of a mild and transient nature that did not meet the predetermined criteria. Only 8 (2.1%; 95% CI, 0.6%–3.4%) subjects met the predetermined criteria for an objective and likely related event. No child experienced more than a mild reaction, 4 of the 8 received oral antihistamines only, and none received epinephrine. Food allergy–related quality of life improved from baseline to 1 month after challenge regardless of outcome ($\eta^2 = 0.2$, $P < .0001$). Peanut skin prick test responses and peanut- and Ara h 2–specific IgE levels were not associated with objective reactivity to peanut ED_{05}. *Conclusion:* A single administration of 1.5 mg of peanut protein elicited objective reactions in fewer than the predicted 5% of patients with peanut allergy. The novel single-dose oral food challenge appears clinically safe and patient acceptable, regardless of the outcome. It identifies the most highly dose-sensitive population with food allergy not otherwise identifiable by using routinely available peanut skin prick test responses or specific IgE levels, but this single-dose approach has not yet been validated for risk assessment of individual patients.

Keywords: eliciting dose, food allergy related quality of life questionnaire, single dose, peanut thresholds, oral food challenges, Voluntary Incidental Trace Allergen Labelling, Peanut Allergen Threshold Study

Clinical implications: The ED_{05} for peanut (1.5 mg of peanut protein) was validated in a multicenter study using a novel single-dose challenge design, which provides a significant quality-of-life benefit for parents of participants and could be adapted to other research or clinical settings.

Abbreviations

DBPCFC: Double-blind, placebo-controlled food challenge
ED: Eliciting dose
ED_{01}: Eliciting dose for a peanut-induced allergic reaction in 1% of subjects studied
ED_{05}: Eliciting dose for a peanut-induced allergic reaction in 5% of the population with peanut allergy
FAQL: Food allergy–related quality of life
FAQL-CF: Food Allergy Quality of Life—Child Form
FAQL-PF: Food Allergy Quality of Life—Parent Form
OFC: Oral food challenge
PAL: Precautionary allergen labeling
PATS: Peanut Allergen Threshold Study
sIgE: Specific IgE
SPT: Skin prick test

Patients with food allergy are clinically selected to participate in diagnostic or research oral food challenge (OFC) protocols that use graded incremental doses administered at short fixed time intervals. Subjects who have experienced anaphylaxis are often not offered routine clinical OFCs and can be excluded from research OFC protocols.[1] It is generally not possible based on graded protocols to determine whether a reaction has occurred to a discrete threshold dose of the allergenic food or has been the result of the cumulative dose consumed by the allergic patient at the time of reaction.

The eliciting dose (ED) for a peanut-induced allergic reaction in 5% of the population with peanut allergy (ED_{05}) has been estimated at 1.5 mg of peanut protein (6 mg of whole peanut) based on the population distribution of threshold doses (children and adults) from graded and blinded oral challenges of 750 patients with peanut allergy.[2–4]

This study aims to assess the precision of the predicted ED_{05} by using a single-dose challenge (6 mg of peanut = 1.5 mg of peanut protein, approximately 1/100th of a peanut kernel) in an unselected group of children with peanut allergy and to validate the processes used to develop the only existing reference doses for peanut, which have been based on the eliciting dose for a peanut-induced allergic reaction in 1% of subjects studied (ED_{01}).[2] It is likely that subjects who react only mildly at the ED_{05} would tolerate the ED_{01} at least as well.[4] This might assist clinicians, regulators, and other stakeholders in risk management for patients with peanut allergy.

Methods

We have already published an in-depth description of the background and methodology of the Peanut Allergen Threshold Study (PATS) study.[5] Additional details are provided below.

Recruitment

This multicenter study involved 3 geographically diverse teaching centers set in university-affiliated hospitals providing local, regional, and national allergy services. The protocol required that the study was discussed fully with every potentially suitable child and family met during routine medical encounters in the clinic or during hospital attendances to minimize recruitment bias. Families who chose not to participate were asked to complete a study-specific "nonparticipant" questionnaire adapted from Osborne et al[6] and to provide written informed consent for their routinely available laboratory data to be examined anonymously in the study. Inclusion and exclusion criteria are shown in Table I.

Table I. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Age between 1 and 18 y inclusive	Medically unfit for challenge according to local unit OFC guidelines/protocol (e.g., high fever or unwell with intercurrent illness)
Evidence of peanut allergy by one of the following:	Oral corticosteroids within 14 days before challenge
History of unequivocal exposure (including accidental) and typical acute allergic reaction within the preceding 2 y and positive peanut SPT response (performed according to local clinical protocols)/ sIgE	Episode of anaphylaxis of any cause in 4 wk before challenge
Positive OFC with peanut performed within 2 years, either open OFC or DBPCFC	Use of antihistamines within 5 d of OFC
Peanut never ingested, but sensitization to peanut greater than the 95% positive predictive value for clinical allergy (i.e., peanut serum IgE ≥ 15 kU/L [by CAP-FEIA] and/or peanut SPT wheal size ≥ 8 mm within 2 mo of the single-dose challenge	Asthma symptoms that are not well controlled, as demonstrated by FEV_1 < 85% of predicted best

Food allergy–related quality-of-life questionnaires

Validated Food Allergy Quality of Life—Parent Form (FAQL-PF) and Food Allergy Quality of Life—Child Form (FAQL-CF) questionnaires were self-administered before OFC (T1) and 1 month after OFC (T2) to assess the effect of this novel single-dose OFC protocol on food allergy–related quality of life (FAQL).[7] FAQL-PF and FAQL-CF are age-appropriate questionnaires that assess the health-related quality of life of children with food allergy. FAQL-PF is completed by a parent of the child with food allergy (0–12 years) and the FAQL-CF is completed by the children themselves (8–12 years) on a 7-point scale ranging from not at all (1) to extremely (7). It has been found to have excellent reliability ($\alpha > 0.9$) and construct, cross-cultural, content, and longitudinal validity. A higher score on either questionnaire reflects higher burden/poorer FAQL. A lower score reflects lower burden/ better FAQL.

Single-dose OFC

The shelf-stable single-dose challenge cookies were manufactured at the University of Nebraska–Lincoln and then distributed to participating clinical centers. Peanut content was determined with the Neogen Veratox Quantitative Peanut Allergen Test (Neogen, Lansing, Michigan). This assay was also used to establish a validated mixing method to achieve a homogeneous incorporation of peanut flour into the formulation, as well as determining whether all ingredients in the formulation were less than the limit of quantitation (2.5 ppm). The stability of the product was established by meeting acceptable criteria for water activity and microbial load. Cookies were stored frozen until use to maintain taste and texture. The single-dose cookie (6 mg of whole peanut = 1.5 mg of peanut protein) consisted of granulated sugar, brown sugar, all-purpose wheat flour, vegetable shortening, salt, baking soda, and light roast, partially defatted peanut flour (Golden Peanut Company, Alpharetta, Georgia). The cookie was eaten under standard open OFC conditions in the

hospital. For subjects allergic to other cookie ingredients (e.g., wheat), the peanut dose of 1.5 mg of peanut protein was administered as the same light roast, partially defatted peanut flour in a vehicle food of the subject's choice. Routine OFC monitoring was performed, according to local clinical practice. Children were observed until 2 hours after OFCs if no symptoms and signs were elicited or until 2 hours after such symptoms and signs had resolved with or without treatment.

Criteria for a positive OFC result

A highly liberal inclusive strategywas used to capture clinical data during the OFCs. Staff were encouraged to make extensive notes, recording any physical or behavioral changes observed or self-reported during the single-dose OFC. Predetermined objective criteria were used because the ED_{05} was predicted on the basis of challenge-associated objective responses only.[1–4] The predetermined objective criteria for a positive OFC result occurring within 2 hours of ingestion were as follows: 3 or more concurrent episodes of noncontact urticaria persisting for at least 5 minutes; perioral or periorbital angioedema; rhinoconjunctivitis, including sneezing; diarrhea; vomiting (excluding gag reflex); or anaphylaxis (with evidence of circulatory or respiratory compromise, such as persistent cough, wheeze, change in voice, stridor, difficulty breathing, and collapse).[8]

Subjective symptoms were also recorded, such as palatal itch, headache, dizziness, bloating, abdominal pain, cramps, muscle aches, aching joints, anxiety, tension, and agitation.

Case definition

When the clinical study was completed, all coinvestigators met in person and reviewed all clinical comments written by staff in each center during the study. The above criteria were applied, and cases were designated "objective" or "subjective" and then as having met or not met the predetermined objective criteria, as above.

Blood test

A blood sample was taken for peanut-specific IgE (sIgE) component analysis (local hospital laboratories with ImmunoCAP [Thermo Fisher, Waltham, Massachsetts], according to the manufacturer's instructions) and quantitative peanut sIgE fluoroenzyme immunoassays 20 minutes after OFCs.

Sample size estimation

Assuming that the observed proportion of the sample that reacts to the single-dose OFC is 5%, a sample size of 375 corresponds to a 95% CI for the population proportion with a lower limit of 3.1% and an upper limit of 7.8% by using the properties of the binomial distribution. The investigators believed that this degree of precision in estimation was sufficient to rule out gross incompatibility between the predicted and observed proportion of participants reacting to the single dose.

Statistics

Data were analyzed with SPSS software (version 22; IBM, Evanston, Illinois). Two-sample *t* tests for continuously valued variables and Pearson χ^2 or Fisher exact tests (for low

prevalence) for binary variables were conducted to determine the extent of any covariate imbalance between participants and nonparticipants. Differences in means and proportions between centers were also examined by using similar statistical methods. The effect of the single-dose protocol on FAQL was analyzed by using multivariable regression analysis.

Partial η^2 (η_P^2) analysis, also known as R^2 analysis, was the effect size produced by the statistical tests used in this study. There are many advantages to including effect size when reporting significant results. Effect size is not influenced by sample size or number of variables. Although a significant result (P value) shows whether an effect exists, it does not reflect the size of the effect. Therefore both the magnitude (effect size) and significance (P value) are essential results to be reported.[9–11] A small effect size is less than 0.08, a medium effect size is less than 0.24, and a large effect size is 0.25 and above.[10]

Ethical approval

This study was approved by the Cork University Hospital Research Ethics Committee (ECM 4 g), Melbourne Royal Children's Hospital Human Research Ethics Committee (HREC App 32166A), and the Partners Human Research Committee (2012P002475). Written informed parental and adolescent consent and younger children's assent (according to local institutional review board age-related requirements) were obtained.

Results

Between October 2013 and February 2015, 518 patients were approached serially for participation (Fig. 1). One hundred thirty-seven subjects were deemed either ineligible or did not wish to take part in the study. Three hundred seventy-eight completed the challenge protocol. Three subjects did not complete the protocol. Comparisons of participants and nonparticipants in each center are shown in Table II. Univariate ANOVA showed no significant age differences between participants and nonparticipants ($P = .62$) controlling for center location ($P = .84$). Sixty percent of the overall sample was male. Twenty-two percent of female subjects approached did not participate compared with 30% of male subjects ($\chi^2 = 6.7$, $P = .035$). There was no difference in participant sex between centers ($\chi^2 = 2.6$, $P = .63$).

A significant association was found between entry criteria and study center location. Twenty-seven percent of Irish subjects had been given a diagnosis of peanut allergy based on the most stringent criterion (positive OFC result) compared with 11% in Australia and only 2.5% in the United States ($P < .001$). However, the diagnostic method did not significantly differ between participants and nonparticipants ($\chi^2 = 3.6$, $P = .17$) or between sexes ($\chi^2 = 6.17$, $P = .19$).

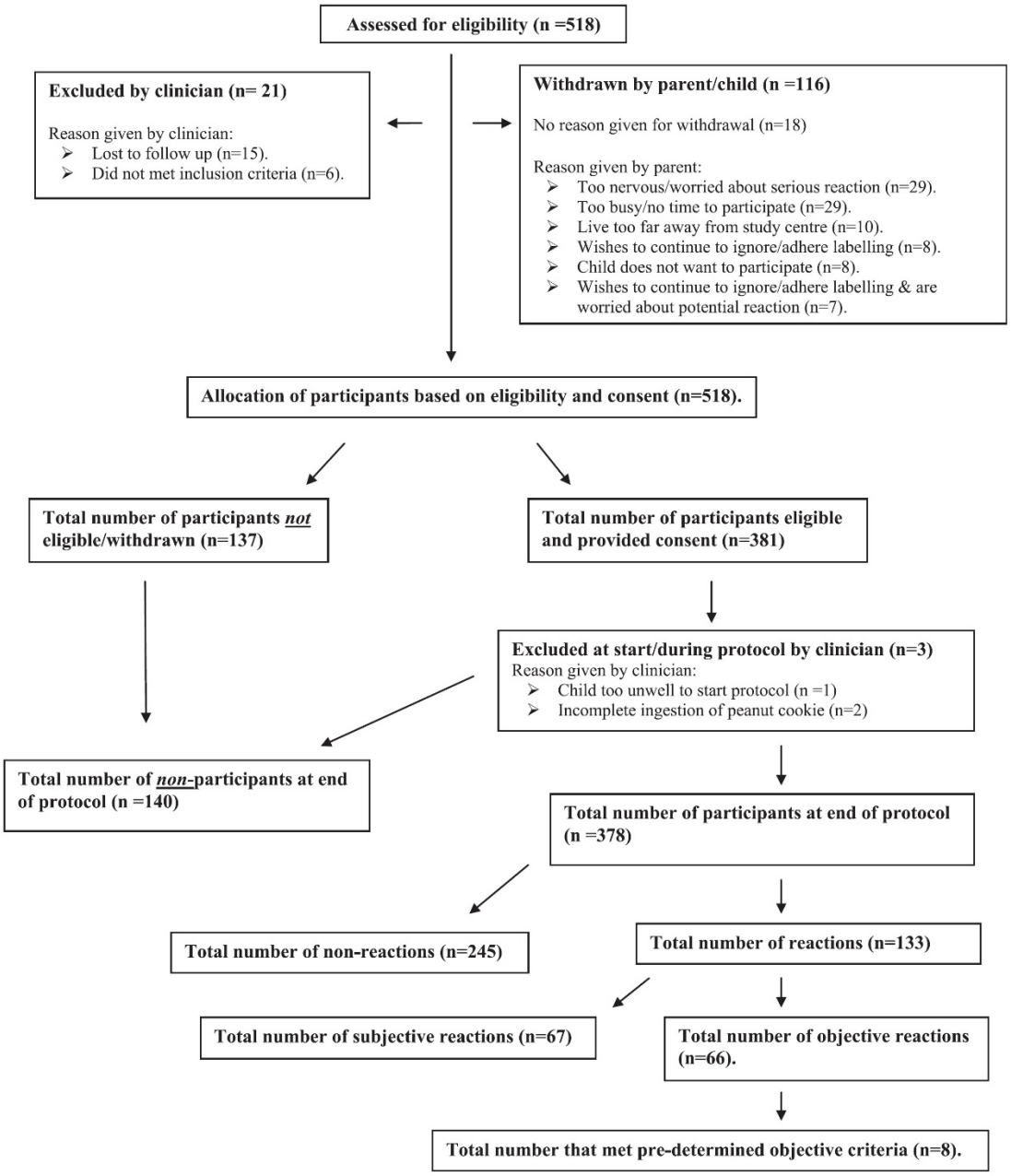

Figure 1. Flow diagram of subject recruitment and participation.

Table II. Demographic comparison of participants with nonparticipants

	Participants			Nonparticipants		
	Cork	Melbourne	Boston	Cork	Melbourne	Boston
Initial no.	124	126	128	63	24	53
Male sex (%)	61	56.3	55.5	60.3	70.8	71.7
Mean age (y)	6.36	7.63	6.55	6.78	8.54	6.65
Final no.*	124	126	128	63	24	35
Inclusion criterion met†						
Typical reaction < 2 y	68	60	74	38	12	19
Positive OFC < 2 y	43	16	2	8	1	2
SPT/sIgE > 95% PPV	13	50	52	17	11	14

PPV, Positive predictive value

*Eighteen participants in Boston did not wish to participate immediately after initial recruitment, and therefore no diagnostic information was gathered.

†Many subjects met both entry criteria 1 and 2, but only the single subject entered in the restricted data file option is reported here.

Reactions to single-dose ED_{05} OFCs

Three hundred eighty-one participants took part in this stage of the study. Two were excluded because of incomplete ingestion of the peanut cookie, and 1 was excluded before starting the protocol because of intercurrent illness, which was evident on clinical examination on the day of study. Three hundred seventy-eight subjects completed the protocol. Three hundred sixty-two (96%) subjects received the single dose in the cookie. The remaining 16 subjects received peanut flour instead in another vehicle food of their choice. There were no significant differences in reaction type between the 362 children who ate the standard cookie and the 16 children who ate the peanut flour in another vehicle ($\chi^2 = 2.21$, $P = .53$).

Two hundred forty-five subjects showed no reaction to the cookie single-dose OFC (Table III). For 133 subjects, a comment indicative of a possible reaction was recorded in the written OFC records. Sixty-seven reported subjective symptoms only. Sixty-six events were considered objective, but 58 of these did not meet the predetermined criteria. The very mild and transient objective symptoms that did not meet the predetermined criteria included nonpersistent, usually single sneeze; nonpersistent, usually single cough; small areas of transient erythema; and fewer than 3 hives lasting less than 5 minutes. Eight participants experienced objective events that met the predetermined criteria (Table IV). All 8 subjects who met the predetermined criteria consumed the cookie and not an alternative vehicle. No participant experienced more than a mild reaction; 4 of the 8 most objectively reacting subjects were treated with oral antihistamines. No other subject was treated, and none received epinephrine.

Table III. Primary outcomes (reaction to single-dose food challenge) per center

	Total	Cork	Melbourne	Boston
Participants				
Active eligible participants (completed OFC)	378	124	126	128
Outcome group				
Total	378	124	126	128
Nonreactors	245	94	65	86
Reactors	133	30	61	42
Subjective reactors	67	19	30	18
Objective reactors				
Total objective	66	11	31	24
Meeting predetermined criteria	8	1	3	4

Table IV. Participants who met the predetermined objective reactivity criteria/case definition

Participant no.	Location	Age (y)	Sex	Diagnostic method	Peanut wheal (mm)	Peanut sIgE (kU$_A$/L)	sIgE rAra h 1	sIgE Ara h 2	Outcome
35	Ireland	11	Female	History of typical exposure and reaction and positive SPT/sIgE result	15	69.10	11.20	59.20	Rhinocon-junctivitis
40	Australia	15	Male	History of typical exposure and reaction and positive SPT/sIgE result	13	2.06	0.53	1.74	Urticaria
43	Australia	9	Male	History of typical exposure and reaction and positive SPT/sIgE result	18	NA	NA	NA	Vomiting
95	Australia	2	Female	Peanut never ingested but positive SPT/sIgE result > 95% PPV	13	NA	NA	NA	Vomiting
31	United States	9	Male	Peanut never ingested but positive SPT/sIgE result > 95% PPV	11	0.36	0.10	0.14	Urticaria
97	United States	2	Male	History of typical exposure and reaction and positive SPT/sIgE result	NA	100.00	14.80	100.00	Urticaria
109	United States	1	Male	History of typical exposure and reaction and positive SPT/sIgE result	NA	57.70	0.10	49.60	Urticaria
124	United States	4	Male	History of typical exposure and reaction and positive SPT/sIgE result	NA	46.70	14.70	16.20	Rhinorrhea

NA, Not applicable; PPV, positive predictive value

Multivariable regression analysis showed no significant differences for age and center, reaction type, or participant/nonparticipant status. The 8 subjects who met the predetermined objective criteria were no different in age than others included in the study (Table IV).

Study center and reaction type were not significantly related to diagnostic entry criteria (χ^2 = 3.39, P = .76). Sex of the subject was not significantly related to reaction type ($\chi 2$ = 4.76, P = .19).

Univariate analyses showed peanut sIgE, Ara h 1, Ara h 2, Ara h 3, Ara h 8, and Ara h 9 sIgE levels, and total IgE levels had no effect on inclusion criterion met or participant/nonparticipant status (P = .21–.99, Table V). Peanut skin prick test (SPT) responses differed between study center location (η_P^2 = 0.02, P = .03) with a small effect size[10] but not for reaction type (P = .25). Irish subjects had the lowest mean wheal size (9.50 mm [SD, 2.66]), and Australian subjects had the highest means wheal size (15mm [SD, 6.47]). No other skin or blood tests were significant for either type of reaction or location (P > .05).

Table V. Reaction type versus mean values for skin and blood tests

	Total IgE	Peanut sIgE	Peanut SPT-induced wheal (mm)	rAra h 1 sIgE	rAra h 2 sIgE	rAra h 3 sIgE	rAra h 8 sIgE	rAra h 9 sIgE
Type of reaction (no.)								
Nonreactor (245)	490.46	28.18	11.69	11.11	22.52	4.88	1.49	0.74
Subjective (67)	1164.89	46.07	15.23	23.42	32.86	9.33	0.74	0.11
Objective (66)	1130.80	39.46	13.60	14.87	31.90	3.13	1.21	0.19
Satisfies predetermined criteria (8)	290.67	45.99	14.00	8.18	45.03	2.35	0.13	0.31

Adherence to precautionary labeling at study entry was significantly lower in Australia, where 76% ignore labeling compared with Ireland (33%) and the United States (36%; χ^2 = 66.21, P < .001). Proxy and self-reported adherence to precautionary allergen labeling (PAL) did not significantly change from T1 to T2 and was unaffected by age of child, study center, or diagnostic criteria met (P = .82–.42).

Food allergy–related quality of life

Baseline scores (before OFC) in the FAQL-PF predicted likelihood of reporting subjective versus objective symptoms (after OFC, P = .001). In effect, children who later experienced subjective symptoms to the single dose of peanut had the most adverse effect on FAQL at baseline (mean, 2.6 [SD, 1.4]). Those who did not experience any reaction had the best FAQL (lowest burden) at baseline (mean, 1.8 [SD, 1.3]). This provides further evidence of the association between clinical and psychological factors in patients with food allergy.

There was a significant main effect for time from T1 to T2 for parent-reported proxy FAQL-PF scores (η_P^2 = 0.24, P = .014), with a medium to large effect size[10] where parents reported an improvement in FAQL for their children from baseline to 1 month after the protocol. There was a significant 3-way interaction between age, sex, and time (η_P^2 = 0.11, P = .014), with a medium effect size.[10] Regardless of the age or sex of the child, parents

reported improved FAQL at T2. Younger boys experienced a higher effect, whereas as age increased, parents reported a greater adverse effect for girls. Diagnostic criteria and type of reaction elicited in the single-dose study were not significant.

Children's self-reported FAQL-CF scores also improved from baseline (T1) to 1 month after the protocol (T2; $\eta_P^2 = 0.5$, $P = .001$) with a very large effect size.[10] Again, there was no effect on FAQL based on inclusion criteria met or type of reaction ($P = .158$).

Discussion

The novel single-dose PATS findings strongly support the safety of the statistically determined ED_{05} based on population dose-distribution modeling[2] for administration to a nonselected patient population. The protocol was very acceptable to families and was clinically very safe. This approach offers the opportunity to identify the most dose-sensitive population of patients with peanut allergy in a safe and efficient manner. It could be adapted for other major allergenic foods.

Population EDs can be estimated by using statistical dose-distribution modeling of individual patient threshold doses.[2–4] ED estimates can vary depending on the choice of model. The single-dose PATS approach serves as a useful way to validate the ED estimates and select the best parametric model. In this single-dose PATS the percentage of patients reacting with the predetermined objective criteria (2.1%) was lower than predicted from the log-normal model (5%; 95% CI, 3.1% to 7.8%). Several reasons could explain the observed difference between the predicted 5% versus observed 2.1% rate. First, selection bias toward more highly sensitive patients could have occurred with the 750 patients with peanut allergy in the modeled data set because many of the patients included in the set were from tertiary allergy clinics, which could contribute to a bias toward a more sensitive population with peanut allergy,[2,3] although this study group of consecutive patients was also recruited in tertiary centers. Second, although objective responses were used in the clinics conducting threshold challenges and the PATS, the objective criteria used to establish the lowest observed adverse effect level for some of the patients might not have been as stringent as the criteria established for the PATS. In particular and among the mild transient reactions that did not meet the predetermined objective criteria, 13 additional patients experienced hives (a single hive in 8 cases, 2 hives in 4 cases, and 3 hives in 1 case, all lasting less than the stipulated 5 minutes). Had these 13 cases been counted as positive responses to the single-dose challenge, the reaction rate would have been 5.5%. Given these possibilities, the log-normal model used appears to be reasonable and appropriately conservative for use in the estimation of EDs for peanut.

Population modeling of individual threshold doses can be used to establish public health measures, such as the control of PAL. In Australia a reference dose for peanut of 0.2 mg of peanut protein was established from estimates of the ED_{01}.[2] The ED_{01} was selected by the Voluntary Incidental Trace Allergen Labelling Scientific Expert Panel because it is predicted to protect 99% of the population with peanut allergy. However, based on the mild and transient responses encountered in PATS, use of ED_{05} as the basis for the peanut reference dose would be a more reasonable and implementable risk management decision.

PAL abounds in many marketplaces, but stakeholders find fault with the approach because use of PAL bears little relationship to actual risk.[12,13] Almost 50% of the study population were routinely ignoring precautionary labeling. PATS has validated the ED_{05}, and therefore the medical and food science communities, manufacturing industry, and public health authorities should consider adopting this model. This would assist in establishing an ED_{05}-based peanut reference dose to be used in quantitative risk assessment to underpin PAL backed by sound scientific evidence, which protects the vast majority of the community of patients with peanut allergy.

No center appeared to have a uniquely more sensitive study population than the other 2, suggesting this protocol and the predetermined criteria used for assessing single-dose OFCs could be used in other centers. Ireland had far more challenge-proved cases than the other centers but lower average ages than the US center, and Australian patients had larger peanut SPT responses and paid less attention to precautionary advisory labels. These intercenter demographic and diagnostic differences did not influence the primary or secondary outcomes of the study.

The predetermined approach to offer the study to all patients with peanut allergy in 3 distinct geographic regions, the comparison of characteristics of participants and nonparticipants, the permissive entry criteria, and the predetermined conservative case definition combine to address the most common criticism of OFC studies. How representative of the general population with peanut allergy are the subjects who volunteered? This study showed children with peanut allergy in each center were broadly similar, that severe reactors were included, and, critically, that participants appeared not to differ clinically from nonparticipants. Although we did not prospectively record previous reaction severity, all subjects were recruited from referred populations seen for their peanut allergy in tertiary/national referral centers, and therefore it is likely the representation of the severe end of the clinical spectrum of peanut allergy in this study population is at least similar to reported peanut allergy norms.

Limitations of the study

Many of the patients recruited were given diagnoses without the gold standard double-blind, placebo-controlled food challenge (DBPCFC). However, the intended recruitment strategy was to recruit relatively unselected but near-certain cases to capture the whole spectrum of cases, which are often not included in incremental dose challenge studies. Our data show no differences in demographic details or serologic findings between participants and nonparticipants or between reactors and nonreactors or between the 8 most certain objective reactors and other groups. The inclusion and exclusion criteria appear to have been well constructed based on established clinical methods used elsewhere, clinical history, and SPT responses and sIgE levels greater than the determined decision points.[14]

Subjects did not undergo placebo challenges but only an active-dose cookie administered once. Placebo doses would have required doubling attendances to more than 700 visits, and we considered the projected likelihood of significant reactivity of around 5% in the single-dose study did not justify a placebo arm. It is notable that 65% of subjects reported no reaction at all to the ED_{05} cookie, despite knowing it was an "active" dose. Intentionally liberal documentation of reported symptoms and having a set of fixed pretest criteria for an

objective reaction allowed post hoc distinction of subjective from objective reactors, although determining the relatedness of any reaction to the single dose was difficult in real time because of the lack of options normally available in routine OFCs, such as waiting longer between doses and repeating doses.[1,14] Subjective reactors had lower pretest FAQL values than objective reactors and nonreactors, which suggests anxiety might play a role in reports of mild/subjective reactions at low doses in the community and in DBPCFCs[15] and also possibly in reactions to placebo doses during DBPCFCs.[16]

PATS was an assessment of low-dose sensitivity in a population of patients with peanut allergy at a single time point, and further studies are needed to assess both population-level and individual subjects' variation in low-dose sensitivity over time. Standard incremental DBPCFCs do not correlate well with the reported severity of community reactions,[17] and dose is only one variable to be considered in the difficult assessment of the severity of food allergy.[18]

The PATS offers a new clinical paradigm and methodology with regard to assessing clinical risk; this current study might define the 5% of patients who are most dose sensitive. It confirms previous findings that validated questionnaires assessing FAQL show patients gain nearly as much from a "failed" OFC as they do from a "passed" OFC, probably because of decreased uncertainty about the next and future reactions.[7] This tangible effect could promote adoption of PATS single-dose peanut challenges in units not currently performing diagnostic multidose OFC.

The single-dose protocol does not replace current clinical food challenges, which are critical for definitive diagnosis of food allergy but would provide extra clinical information of patients' level of risk related to dose and could help inform consumer choices and physician advice to patients regarding PAL.[13,15] Single-dose challenges could be done before starting a progressive clinical food challenge to identify the most highly sensitive patients and reduce any risks associated with the use of higher doses used in clinical food challenges. PATS suggests clinical validation of other allergenic food sources could be addressed in similar studies in which the population dose distribution has been modeled by using sufficient threshold data. Clinicians might be able to use PATS single-dose OFCs widely because they are easier to perform than routine diagnostic OFCs or DBPCFCs.

Conclusion

The novel single-dose OFC based on the statistical dose-distribution analysis of past challenge trials is a clinically safe and efficient approach to identify the most highly dose-sensitive population of patients with food allergy, and it improves food allergy–related quality of life. The validation of the ED_{05} will also assist regulators, public health agencies, and manufacturers in the establishment of approaches to allergen management that will protect the vast majority of consumers/patients with food allergy.

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