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ORIGINAL ARTICLE

Peanut Oral Immunotherapy in Children with High-Threshold Peanut Allergy

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Abstract

BACKGROUND Approved therapeutics for peanut allergy are not designed for the many patients with allergic reactions to more than one peanut.

METHODS We randomly assigned (1:1) participants 4 to 14 years of age reacting to a challenge of between 443 mg and 5043 mg of peanut protein to peanut oral immunotherapy (P-OIT) using home-measured peanut butter versus peanut avoidance. The primary end point was the difference between groups in the proportion tolerating a two-dose-level increase or 9043 mg of peanut protein. For ingestion participants tolerating 9043 mg, sustained unresponsiveness (tolerance off treatment) was tested after 16 weeks of ad lib ingestion followed by 8 weeks of abstinence.

RESULTS Of 73 participants, 38 were randomly assigned to P-OIT and 35 to avoidance. Thirty-two of 38 participants in the ingestion group (84.2%) and 30 of 35 in the avoidance group (85.7%) underwent the primary outcome food challenge. The primary analysis with prespecified multiple imputation for missing values showed 100% success for ingestion versus 21.0% for avoidance (between-group difference, 79.0 percentage points; 95% confidence interval [CI], 64.6 to 93.5; P<0.001). All 32 treated and 3 out of 30 avoiders (10%) tolerated 9043 mg. In the intention-to-treat analysis, sustained unresponsiveness occurred in 68.4% (26/38) on P-OIT versus 8.6% (3/35) tolerating 9043 mg among those avoiding (between-group difference, 59.9 percentage points; 95% CI, 42.4 to 77.3). No dosing reactions were greater than grade 1 severity, and no serious adverse events were reported.

CONCLUSIONS In this trial of P-OIT using store-bought, home-measured peanut versus peanut avoidance in high-threshold peanut allergy, those treated achieved significantly higher rates of desensitization with a durable response off treatment. (Funded by the National Center for Advancing Translational Sciences [UL1TR004419] and the National Institute of Allergy and Infectious [U19AI136053]; ClinicalTrials.gov number, NCT03907397.)

Introduction

Peanut allergy affects an estimated 2.2% of children and 1.8% of adults.[1,2] Management options include strict avoidance or treatment with U.S. Food and Drug Administration (FDA)–approved therapy such as the anti-immunoglobulin E

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(IgE) biologic omalizumab or pharmaceutical grade peanut oral immunotherapy (P-OIT).[3,4] Research evaluating these therapies and others such as epicutaneous immunotherapy[5,6] or sublingual immunotherapy,[7] or combinations of therapies such as omalizumab used with P-OIT,[8,9] have focused on participants with a low tolerance to peanut protein, that is, those patients who react to a dose of 100 mg or less of peanut protein during a graded double-blind, placebo-controlled oral food challenge (DBPCFC). There are very few data relevant to the large fraction of patients with peanut allergy whose reaction to peanut is only manifested when amounts greater than one half of a peanut, approximately 100 mg of peanut protein, are ingested.[10,11] To address this void, we conducted a randomized controlled trial using inexpensive home-measured peanut butter to assess the benefits of P-OIT in children who do not manifest symptoms of peanut allergy until they ingest more than the amount of such protein found in the equivalent of one half of a single peanut, so-called high-threshold responders to DBPCFCs.

Methods

TRIAL DESIGN AND PARTICIPANTS

The ChAllenging to Food with Escalating ThrEsholds for ReducIng Food Allergy (CAFETERIA) trial is a single-center, phase 2, prospective, two-group, parallel-group, 24-week, randomized controlled open-label trial of P-OIT using home-purchased, home-measured peanut as the treatment versus avoidance of peanut as the control. The trial included children 4 to 14 years of age (ages where spontaneous resolution is unlikely and retention in a prolonged trial would be high) who were strictly avoiding peanut and had a history of sensitization defined as peanut serum IgE concentration greater than 0.35 kU_A/l, and during a screening DBPCFC were able to ingest 143 mg or more of peanut protein but less than 5043 mg of peanut protein (cumulative amount) without dose-limiting reaction symptoms. A key exclusion criterion was a serum peanut-specific IgE antibody level greater than 50 kU_A/l (full criteria are in the Supplementary Protocol, Sections 4.2 and 4.3). Commercial peanut products were used under an FDA Investigational New Drug Application (Sicherer, 18399). This trial was approved by the Program for the Protection of Human Subjects at the Icahn School of Medicine at Mount Sinai and monitored by an independent data and safety monitoring board. Written informed consent/assent was obtained from all participants.

RANDOM ASSIGNMENT AND INTERVENTION

Participants underwent a screening DBPCFC using 12% fat, lightly roasted peanut flour to determine their threshold. Dosing was according to the modified PRACTALL protocol[12] with doses of 3, 10, 30, 100, 300, 600, 1000, and 3000 mg, and an additional dose of 4000 mg of peanut protein. DBPCFCs, conducted by staff not informed of treatment allocation, were considered positive when symptoms fulfilled prespecified criteria (see Supplementary Appendix, page 4). Those reacting at the 300-, 600-, 1000-, or 3000-mg dose were eligible for random assignment (Fig. 1).

Participants were randomly assigned in a 1:1 ratio to ingest or avoid peanut. The random assignment was stratified according to age (4 to less than 10 years of age vs. 10 to 14 years of age) and cumulative reaction dose at the screening DBPCFC. A random permuted block design of sizes of four and six was employed for each combination of stratification factors to generate the random assignment scheme.

Participants randomly assigned to P-OIT returned for an observed ingestion of peanut butter with a dose of approximately 20 to 35% of the cumulative reaction dose (Fig. 1). To proceed with daily dosing, the participant had to tolerate a one eighth level teaspoon of peanut butter (approximately 137 mg of protein). Participants could substitute commercially available, dose-equivalent forms of peanut protein,[13] such as candies, once they were tolerating one half teaspoon or more of peanut butter. Participants returned every 8 weeks to attempt a supervised feeding of the next higher amount. If successfully consumed, they continued the one-step-higher amount daily. A repeat DBPCFC was performed 8 weeks after reaching 1 tablespoon (approximately 3396 mg of protein), or at 72 weeks. A repeat DBPCFC was performed in the avoidance group at a time calculated according to an algorithm to ensure similar lengths between initial and primary outcome DBPCFC between the groups.

Participants in the ingestion group tolerating the full challenge amount added peanut to their diet for 16 weeks without daily dosing, but with instructions to consume at least 2 tablespoons of peanut butter or equivalent per week and then avoid peanut entirely for 8 weeks, followed by a DBPCFC to assess for sustained unresponsiveness.

Participants underwent skin prick testing (SPT), serum testing for peanut-specific antibody levels (ImmunoCAP™, ThermoFisher Scientific, Inc.), and completed a food allergy quality-of-life survey prior to the screening DBPCFC, 16 weeks after (excepting SPT), and at the DBPCFC performed to assess desensitization in the ingestion group or threshold at the primary outcome assessment for

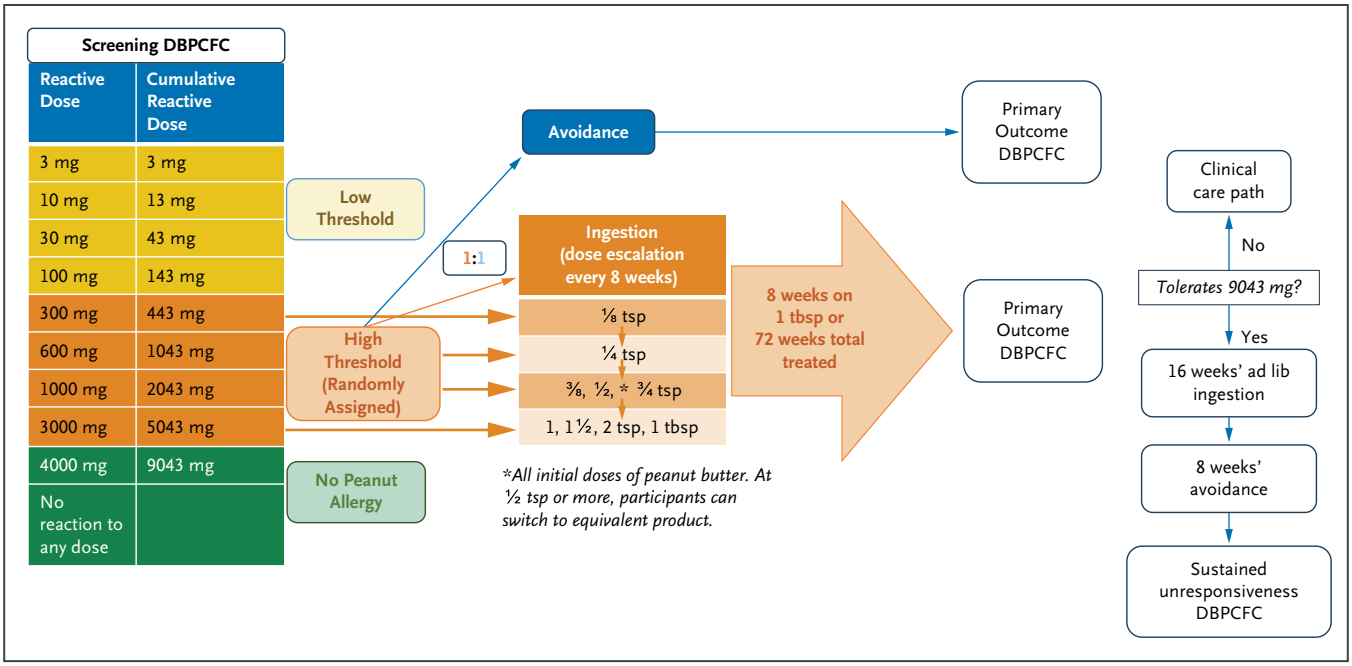

Figure 1. Trial Scheme.

DBPCFC denotes double-blind, placebo-controlled oral food challenge; tbsp, tablespoon; and tsp, teaspoon.

avoiders. The Food Allergy Quality of Life — Parental Burden (FAQL-PB) questionnaire was used to measure quality of life.[14] The instrument, when analyzed as a sum of item scores, ranges from 0 to 102, with 102 indicating the worst quality of life. The minimally important difference is not known. The SPT mean wheal diameter was measured at 15 minutes and calculated as the average of the largest diameter and the corresponding longest perpendicular diameter, with the mean wheal diameter defined as the difference between the mean wheal diameter for the peanut extract and the negative control. Participants were called monthly to review peanut exposure and adverse events. Symptoms were collected using MedDRA-preferred terms (MedDRA.org). The severity of adverse events was graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (NCI-CTCAE, 5.0), except anaphylaxis, which was graded according to the severity scale included in the Supplementary Protocol, Study Definitions page.

END POINTS

The primary end point was the difference between the ingestion and avoidance groups in the percentage of children who by the primary outcome DBPCFC, tolerated a dose at least two steps higher than their baseline DBPCFC or the full dose (9043 mg) of peanut protein. The key secondary clinical end points were the following: the percentage of children in the ingestion group who tolerated 9043 mg at the final DBPCFC (sustained unresponsiveness) or in the avoidance group at the primary outcome DBPCFC (natural tolerance); safety parameters; and quality of life. Additional outcomes included change over time in peanut and *Arachis hypogaea* 2 (Ara h 2)–specific IgE, peanut and Ara h 2–specific IgG4, and SPT mean wheal size. Additional prespecified mechanistic and exploratory objectives outlined in the Supplementary Protocol (Section 3.2.2) are not reported herein.

STATISTICAL ANALYSIS

Our initial planned trial design was to randomly assign 98 participants. This sample size calculation was based on an estimated 10% response rate in the avoidance group, an absolute increase of 45 percentage points for the ingestion group, a drop-in rate (avoiders undertaking ingestion) of 10%, and a drop-out rate (peanut consumers discontinuing treatment) of 20%. Having 98 randomly assigned participants provided 90% power to detect a difference of 31.5 percentage points (accounting for crossovers) based on a 0.05-level continuity-corrected chi-square test. The Covid-19 pandemic caused a temporary shutdown and slowed enrollment. Considering trial timelines and feasibility,

a blinded sample size reestimation was conducted when 29 participants were randomly assigned (November 2020). The observed drop-out rate was 14%, and the drop-in rate was 0%. The sample size was modified to 72 based on a 5% drop-in rate that provided 85% power to detect a between-group difference of 33.75 percentage points (accounting for crossovers), assuming that the drop-out rate (20%) and success rates (55% for ingestion; 10% for avoidance) remained unchanged from the original design.

The hypothesis for the primary end point was tested using a continuity-corrected chi-square test. Participants with missing primary end point data had their DBPCFC cumulative tolerated dose imputed through multiple imputation, assuming a missing-at-random mechanism. The imputation model included random assignment, age, sex, baseline reactive dose, and clinical severity during baseline DBPCFC, as well as peanut-specific IgE levels at baseline and week 16. Planned sensitivity analyses were performed to assess the validity of the imputation model.

For the analysis of the sustained unresponsiveness or natural tolerance end point, a continuity-corrected chi-square test was used, and missing outcome values were imputed as failures. The change over time in other secondary end points, including quality of life, SPT mean wheal size, and IgE and IgG4 ($\log_{10}$-transformed) levels, were assessed with longitudinal linear mixed-effects models. Details regarding the analysis of the primary and secondary end points are provided in the statistical analysis plan (see Supplementary Appendix, Section 6.5).

All analyses were performed at the two-sided 0.05 significance level using SAS version 9.4 (SAS Institute Inc.) and R version 4.3.3 in the intention-to-treat population. There was no prespecified method to control the type 1 error rate for multiple testing across secondary end points. As such, the widths of 95% confidence intervals (CIs) have not been adjusted for multiplicity and should not be used to infer definitive treatment effects.

Results

PARTICIPANTS

From August 2019 through April 2022, 129 participants initiated the screening DBPCFC (Fig. 2). Among them, 23 reacted at a low threshold (<143 mg), 30 did not react or reacted at a threshold too high for random assignment (≥9043 mg), and 3 did not complete the DBPCFC; leaving 73 eligible for random assignment, with 38 randomly assigned to ingestion and 35 to avoidance. Table 1 shows the characteristics of the randomly assigned participants. Of the total, the median (25th and 75th percentiles) age was 7 (5–10) years, 61.6% (45/73) were male, and 57.5% (42/73) were White, 19.2% (14/73) were Asian, 1.4% (1/73) were Black, and 21.9% (16/73) were multiracial.

PRIMARY END POINT: DESENSITIZATION

Thirty-two of 38 participants in the ingestion group (84.2%) and 30 of 35 in the avoidance group (85.7%) underwent the primary outcome DBPCFC. Among the six who withdrew from the ingestion group, one withdrew because of dose-related symptoms (nausea and stomach discomfort), while the other five withdrew for anxiety, distaste, scheduling conflicts, relocation, and withdrawal by parent. The median time from the baseline to the primary outcome DBPCFC ranged from 7.8 to 16.8 months based on the baseline reaction dose and was similar for those avoiding or ingesting (Fig. S1).

All 32 ingestion group participants undergoing DBPCFC met the primary end point by tolerating 9043 mg of protein (100%); whereas in the avoidance group, 6 of 30 met the end point (20%), but only 3 (10%) tolerated the 9043-mg ingestion. The analysis of the primary end point included both observed and imputed data for missing values due to withdrawal. In this analysis, the estimated success proportion was 100% for the ingestion group and 21.0% for the avoidance group (between-group difference, 79.0 percentage points; 95% CI, 64.6 to 93.5; P<0.001) (Fig. 3A). In a sensitivity analysis considering missing values as failures, the success rate was 84.2% (32/38) in the ingestion group and 17.1% (6/35) in avoiders. In another (unplanned) sensitivity analysis that assumed failures for missing values in the ingestion group and successes in the avoidance group, the most conservative analysis, the percentage of participants meeting the primary end point was 84.2% (32/38) in the P-OIT group versus 31.4% (11/35) in the avoidance group. Additional sensitivity analyses are reported in Table S1.

Figure 3C shows the change in the cumulative tolerated dose from baseline to primary outcome DBPCFC. The median baseline cumulative tolerated dose was 443 mg in both groups. The median increased to 9043 mg in the ingestion group and remained at 443 mg in the avoidance group at the primary outcome DBPCFC. Of the 30 participants in the avoidance group undergoing primary outcome DBPCFCs, 5 (16.7%) reacted at a dose below the threshold

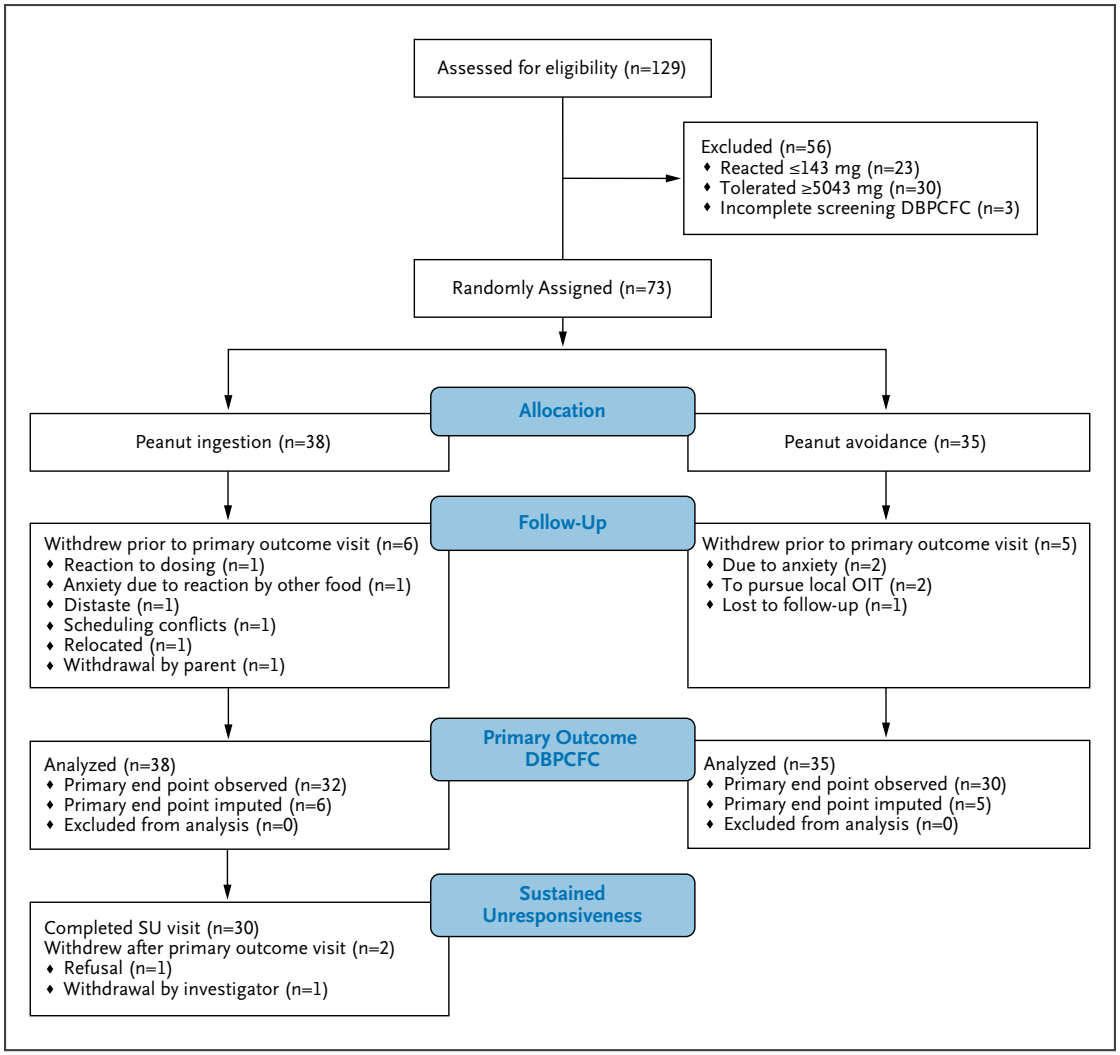

Figure 2. CONSORT Flow Diagram.

CONSORT denotes Consolidated Standards of Reporting Trials; DBPCFC, double-blind, placebo-controlled oral food challenge; OIT, oral immunotherapy; and SU, sustained unresponsiveness.

for random assignment, 3 at 43 mg, and 2 at 143 mg; these 5 had originally reacted at 443 mg. Overall, 11 out of 30 (36.7%) reacted at a lower dose than at baseline, 8 out of 30 (26.7%) at the same dose, and 11 out of 30 (36.7%) at a higher dose.

Participants were queried regarding adherence and two met prespecified criteria for possible therapy discontinuation due to nonadherence to protocol procedures. Nonadherence was noted in a participant in the ingestion group who up-dosed at home during Covid-19 with a regimen similar to what was planned per protocol and later stopped dosing. This participant was withdrawn by the investigator after the primary outcome DBPCFC. Another participant inadvertently up-dosed and was provided reeducation and remained in the trial. No participants on avoidance reported self-dosing.

SUSTAINED UNRESPONSIVENESS AND NATURAL TOLERANCE

The 32 participants in the ingestion group were eligible to undertake a DBPCFC to determine sustained unresponsiveness, and 30 agreed to undergo the test. One participant refused, and another was withdrawn by the investigator after the primary outcome DBPCFC for nonadherence. Of these 30, 26 (86.7%) met the sustained unresponsiveness end point. Of the four who had symptoms, all were grade

Table 1. Demographics and Baseline Allergy Test Results.*

Baseline Demographic or Test Result	Peanut Ingestion (N=38)	Peanut Avoidance (N=35)	ASMD†
Age — years	6.0 (5.0–10.0)	7.0 (4.0–11.0)	0.0557
Female sex — no. of patients (%)	19 (50.0)	9 (25.7)	0.5172
Race — no. of patients (%)‡			0.5406
Asian	10 (26.3)	4 (11.4)	
Black or African American	1 (2.6)	0 (0.0)	
White	18 (47.4)	24 (68.6)	
Multiracial	9 (23.7)	7 (20.0)	
Hispanic or Latino — no. of patients (%)	5 (13.2)	2 (5.7)	0.2567
Baseline reactive dose — no. of patients (%)			0.2028
443 mg	17 (44.7)	16 (45.7)	
1043 mg	8 (21.1)	8 (22.9)	
2043 mg	8 (21.1)	5 (14.3)	
5043 mg	5 (13.2)	6 (17.1)	
Symptoms at baseline DBPCFC — no. of patients (%)			
Cutaneous	24 (63.2)	19 (54.3)	0.1809
Gastrointestinal	26 (68.4)	25 (71.4)	0.0656
Respiratory	4 (10.5)	3 (8.6)	0.0666
Skin prick test — mm	8.0 (6.5–11.0)	9.0 (7.0–9.5)	0.1114
Peanut IgE level — kU_A/l	5.5 (2.4–8.7)	4.6 (2.0–9.1)	0.0231
Peanut IgG4 level — mg_A/l§	0.4 (0.1–1.2)	0.4 (0.1–1.4)	0.0978
Ara h 2 IgE level — kU_A/l	3.8 (1.2–6.9)	2.6 (1.5–6.3)	0.1145
Ara h 2 IgG4 level — mg_A/l§	0.020 (0.007–0.060)	0.050 (0.007–0.110)	0.2866

* Continuous variables are expressed as median (25th percentile, 75th percentile). Categorical variables are expressed as counts and percentages. Ara h 2 denotes *Arachis hypogaea* 2; ASMD, absolute standardized mean difference; DBPCFC, double-blind, placebo-controlled oral food challenge; Ig, immunoglobulin.

† ASMDs are the absolute difference in rank-based means or percentages divided by the pooled standard deviation. Rank statistics were used since continuous baseline variables showed skewness. An ASMD of 0.10 or less is considered an ideal balance; an ASMD of 0.20 or less is considered an acceptable balance.

‡ Race was reported by participants.

§ One participant was missing peanut and Ara h 2 IgG4 levels at baseline. There was no missingness in any other baseline measures.

1, treated only with antihistamines and occurred at doses of 9043 mg (n=1), 5043 mg (n=2), and 1043 mg (n=1). This is compared with 3 of the 30 (10%) in the avoidance group tolerating 9043 mg of peanut protein at the primary outcome DBPCFC; we believe that this represented naturally occurring tolerance. In the analysis of the secondary sustained unresponsiveness/natural tolerance end point, which considered all missing values as failures, the success rate was 68.4% (26/38) in the ingestion group compared with 8.6% (3/35) in the avoidance group (between-group difference, 59.9 percentage points; 95% CI, 42.4 to 77.3) (Fig. 3B).

Quality of Life

Quality-of-life scores appeared to be similar between groups (estimated difference in mean change from baseline, 1.44; 95% CI, −6.20 to 9.08). Both groups improved with an estimated mean (SE) change from baseline in the FAQL-PB questionnaire of −7.78 (2.68) for the ingestion group and −9.23 (2.77) for the avoidance group.

LABORATORY BIOMARKERS

Skin prick tests to peanut at the primary outcome DBPCFC visit decreased from baseline for the ingestion group, but not in the avoidance group (estimated difference in mean change from baseline, −2.57 mm; 95% CI, −4.32 to −0.82) (Fig. 3D). The observed median (25th and 75th percentiles) peanut-specific IgE and Ara h 2–specific IgE were 5.1 kU_A/l (2.6–6.8) and 2.6 kU_A/l (0.7–4.3), respectively, at the primary outcome DBPCFC visit in the ingestion group and 7.9 kU_A/l (5.4–13.0) and 3.3 kU_A/l (1.3–8.7) in the avoidance group. Peanut-specific IgG4 in the ingestion group was 5.2 mg_A/l (3.0–16.1) and 0.6 mg_A/l (0.2–1.3) in the avoidance group (Fig. S2).

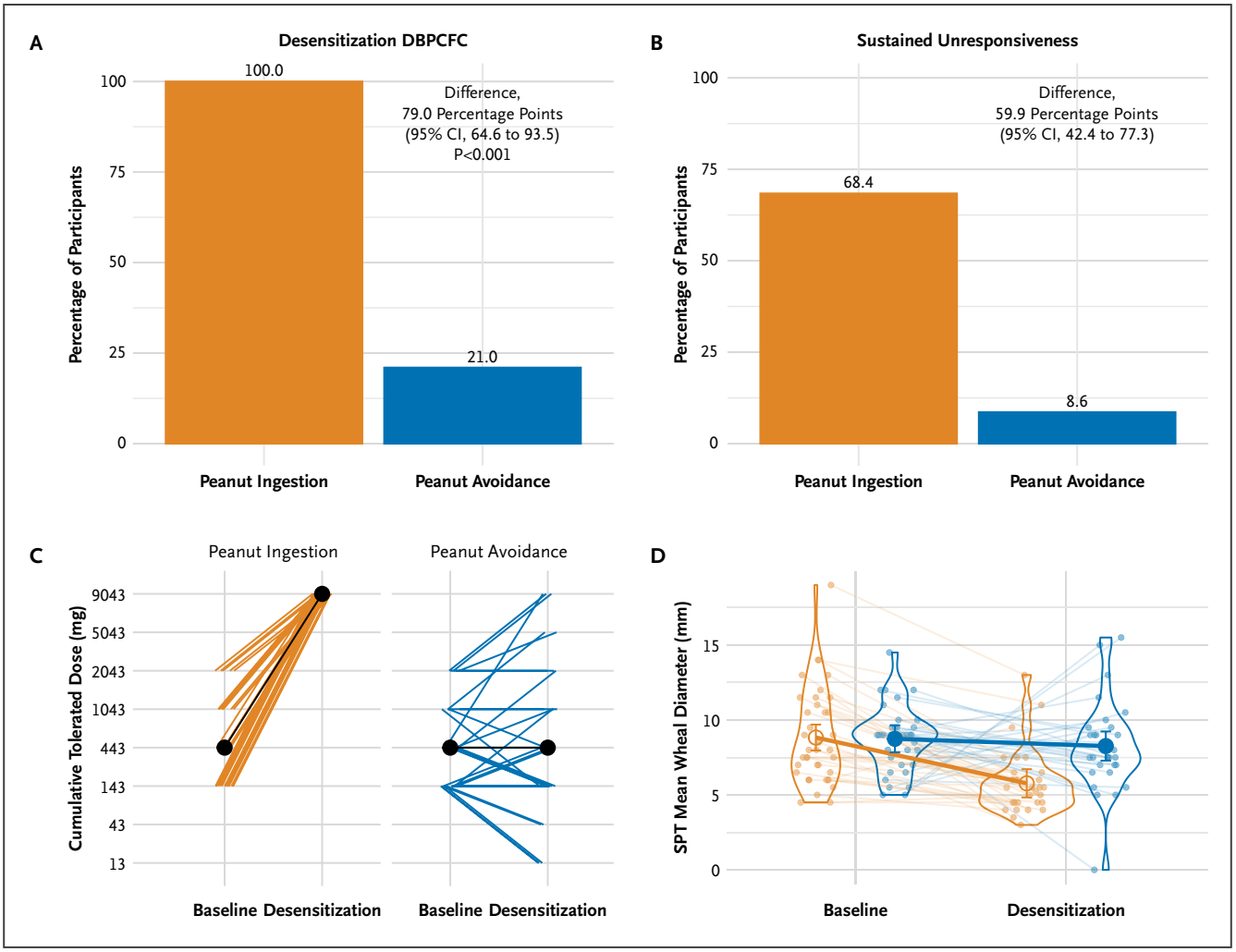

Figure 3. Primary and Secondary End Points.

Panel A depicts the percentage of participants who tolerated a dose at least two steps higher than their baseline double-blind, placebo-controlled oral food challenge (DBPCFC) or the full dose (9043 mg) of peanut protein at the primary outcome DBPCFC. Estimates are based on the analysis of multiply imputed data. Panel B depicts the percentage of participants who achieved sustained unresponsiveness in the peanut ingestion group and natural tolerance in the peanut avoidance group. Missing data are considered failures. Panel C depicts the change in the cumulative tolerated dose for each participant between the baseline and primary outcome DBPCFC. The black dot represents the median cumulative tolerated dose at each visit. Panel D depicts the distribution of the mean wheal diameter on skin prick tests. The big circle, near the center of each plot, represents the estimated mean for each group at each visit based on a linear mixed-effects model that includes a random intercept and the fixed effect of random assignment, time, and the interaction between group and time. CI denotes confidence interval; DBPCFC, double-blind, placebo-controlled oral food challenge; and SPT, skin prick testing.

Safety Assessments

Among the 126 participants completing baseline DBPCFCs, there were 102 who experienced allergic reactions during the peanut ingestion (none reacted to placebo), and all but two had grade 1 adverse reactions (Table S2). During supervised dosing visits, there were six allergic reactions during 269 visits; all were grade 1, and one participant was treated with epinephrine for a cough and rhinorrhea (Table S3). While participants were on home avoidance or dosing, there were 36 participants reporting adverse events, 25 among the ingestion group and 11 among avoiders (Table 2). Overall, 208 of 270 events were dosing related. None of the dosing reactions was over grade 1. Eight participants were administered epinephrine, four of them were in the

Table 2. Adverse Events during Dosing or Home Avoidance.

System Organ Class and Preferred Term	Peanut Ingestion (N=38)		Peanut Avoidance (N=35)	
	Participants — no. of patients (%)	Events — no. of events	Participants — no. of patients (%)	Events — no. of events
Gastrointestinal disorders	24 (63.2)	195	8 (22.9)	13
Abdominal discomfort	9 (23.7)	20	1 (2.9)	1
Abdominal pain	4 (10.5)	8	1 (2.9)	1
Nausea	2 (5.3)	2	0 (0.0)	0
Oral pruritus	17 (44.7)	152	8 (22.9)	9
Vomiting	8 (21.1)	11	2 (5.7)	2
Projectile vomiting	1 (2.6)	2	0 (0.0)	0
Immune system disorders	12 (31.6)	19	8 (22.9)	14
Anaphylactic reaction*	0 (0.0)	0	2 (5.7)	2
Lip edema	1 (2.6)	1	1 (2.9)	1
Pruritus allergic	1 (2.6)	2	4 (11.4)	4
Urticaria	10 (26.3)	16	6 (17.1)	7
Respiratory, thoracic, and mediastinal disorders	7 (18.4)	12	4 (11.4)	8
Cough	2 (5.3)	3	1 (2.9)	1
Rhinorrhea	4 (10.5)	6	2 (5.7)	3
Throat tightness	3 (7.9)	3	2 (5.7)	3
Wheezing	0 (0.0)	0	1 (2.9)	1
Skin and subcutaneous tissue disorders	3 (7.9)	6	2 (5.7)	3
Dermatitis atopic	2 (5.3)	2	1 (2.9)	1
Erythema	2 (5.3)	4	1 (2.9)	2
Total	25 (65.8)	232	11 (31.4)	38

*Two participants had an anaphylactic reaction (not related to the timing of study treatment dosing). One participant's reaction was consistent with a food allergy reaction at a restaurant for a meal that was not supposed to contain peanut. A second wheat-allergic participant ate French fries that were later found to contain wheat.

dosing group, but none of the reactions were temporally associated with therapeutic dosing. There were two anaphylactic reactions following accidental ingestions in the avoidance group, one to wheat and another to an unknown trigger. There were no deaths, no serious adverse events, no reports of symptoms consistent with eosinophilic esophagitis, and dose-related gastrointestinal symptoms occurred in 24 out of 38 (63.2%) people in the active treatment group and 8 out of 35 (22.9%) people in the avoidance group.

Discussion

In this trial of P-OIT in children 4 to 14 years of age having a baseline threshold of peanut allergy over 143 mg, treatment with home-measured, supermarket-purchased peanut products, to a maintenance daily dose of 3400 mg, was superior to standard of care avoidance. The primary planned analysis with multiple imputation showed that 100% of those ingesting and 21% avoiding peanut products reached the DBPCFC-established primary end point. No children treated with peanut ingestion had serious reactions from the treatment, and one received epinephrine during supervised dosing visits. Our data show that treatment of children 4 to 14 years of age, who had a high baseline threshold of peanut allergy, were able to safely ingest a meal-sized portion of peanut following treatment with low-cost, supermarket-purchased products.

Among those treated in our trial, 26 of 30 (87%) continued to tolerate 9043 mg after 8 weeks of avoidance. Testing for sustained unresponsiveness off P-OIT treatment has been reported in several studies of peanut allergy, typically without formal prespecified criteria, and in children with various thresholds, time and dose of treatment, and periods off therapy,[15-18] including a case series of children identified as being "low-dose tolerant, high-dose mild responders."[19] Two trials were designed to formally test sustained unresponsiveness. In a trial of peanut allergic patients, median age 11 years, having reacted to a dose equal to or less than

500 mg on the baseline oral food challenge (OFC), and treated with up to 4-g daily-maintenance P-OIT, 85% tolerated a 4-g food challenge at week 104.[20] Among a subset randomly assigned to stop therapy, 35% achieved this threshold 13 weeks later, and only 20% maintained the threshold at 26 weeks. The authors of another trial speculated that younger children are more likely to attain remission when so treated.[21] In their trial of children 1 to 4 years of age, reacting to a dose equal to or less than 500 mg at baseline, P-OIT was administered for 134 weeks with a maintenance goal of 2 g.[21] Overall, 71% on treatment tolerated a 5-g peanut OFC, but only 21% maintained this threshold at a remission end point OFC after 6 months of avoidance. In contrast to these trials of children with a relatively low threshold of peanut allergy, our high-threshold participants were very likely to maintain their protection. We designed our testing to mimic what might occur in real life, where after the end of treatment, participants were asked to stop dosing and to ingest peanut ad lib for 4 months and then stop entirely for 2 months. The four children who did not continue to tolerate the 9 g of peanut protein had only grade 1 symptoms that were treated with antihistamines.

Although a commercialized form of peanut protein for P-OIT is available, it is expensive, time consuming to use, and carries risks.[22,23] Our trial is unique in focusing on children with a higher threshold, a large and generally neglected cohort of patients, who are typically instructed to avoid peanut.[24] One could speculate that this high-threshold group, although burdened with needing to avoid peanut, can achieve an element of safety against accidental exposure by a dosing protocol as described herein. As data to inform decisions have been previously unavailable, allergists variably have instructed patients with a demonstrated higher peanut threshold to either strictly avoid peanut, allow some dietary inclusion, or seek P-OIT.[25] Our data suggest that peanut avoidance may result in some children becoming more sensitive, while in our small sample this did not occur in those receiving active treatment.

Our trial has limitations. The trial population is representative of the U.S. pediatric peanut allergy population in terms of sex, but the trial enrolled a lower number of Black and Hispanic children and a higher number of Asian children than would be expected for the U.S. population of children with food allergies (Table S4). Having fewer Black participants than would be representative of those affected is an ongoing limitation in food allergy trials.[3-6] Having an exclusion of those with peanut-specific IgE of greater than 50 kU_A/l was chosen to reduce screen failures for random assignment,[4] but limits generalizability. The trial was designed to examine a potential real-world approach and, therefore, the treatment could not be masked, although the determination of threshold end points used the current clinical standard DBPCFCs. Ingestion and avoidance groups experienced improved quality of life, with no impact of the trial intervention. This patient-related outcome measure is recognized to have limitations because it was not developed or validated as a tool for the determination of outcomes in clinical trials.[26] Finally, this was a single-site trial, which could affect generalizability.

In this small phase 2 trial, we showed in children 4 to 14 years of age who were allergic to peanut but could tolerate more than 143 mg of protein at baseline, that high-dose, store-bought, home-measured P-OIT was effective in raising their threshold to serving size amounts of peanut with a durable response off treatment for the majority. In contrast, as a group, those untreated did not experience a change in their threshold of reaction, and one third experienced a reduction in their threshold. Further research is needed to address long-term outcomes and to apply this strategy to other food allergens.

Disclosures

Author disclosures and other supplementary materials are available at evidence.nejm.org.

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