

Long-Term Outcome of Peanut Oral Immunotherapy Facilitated Initially by Omalizumab



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What is already known about this topic? In highly sensitive peanut-allergic patients, adjunctive omalizumab therapy can facilitate oral immunotherapy (OIT). Complications of OIT can include allergic reactions and eosinophilic esophagitis.

What does this article add to our knowledge? Almost half the patients stopped OIT within 72 months. Adverse reactions developed in some patients, despite significant drops in peanut-IgE. However, elevated Arah2-IgE at month 12 was associated with OIT discontinuation.

How does this study impact current management guidelines? Omalizumab may be considered as adjunctive therapy for peanut OIT. Long-term OIT is associated with adverse reactions, despite a marked decrease in peanut-specific IgE. Elevated peanut-IgE and Arah2-IgE few months after omalizumab cessation are associated with OIT discontinuation.

BACKGROUND: We successfully used omalizumab to facilitate peanut oral immunotherapy (OIT) in children with reactivity to ≤ 50 mg peanut protein and with high peanut IgE (median, 229 kU/L).

OBJECTIVE: We report on long-term OIT outcomes in these patients, including dosing changes, adverse events, peanut immunoglobulin changes, and quality of life (QoL).

METHODS: Patients were followed for up to 72 months (67 months of maintenance). Outcomes were collected on peanut dose amount, form, and frequency, as well as adverse events, (QoL), and laboratory studies.

RESULTS: Of 13 patients initially enrolled, 7 patients (54%) continued on peanut OIT through month 72; 6 (46%) discontinued therapy because of adverse reactions. Maintenance

peanut protein dose varied between 500 and 3500mg. Most patients consumed different peanut-containing products. All patients experienced at least 1 adverse event, and 1 patient developed eosinophilic esophagitis. Peanut-IgE, Arah1-IgE and Arah2-IgE, peanut-SPT, peanut-IgE:IgE ratio, and Arah2-IgE:Arah2-IgG4 ratio decreased on OIT. Peanut-IgG4, Arah1-IgG4, and Arah2-IgG4 initially increased on OIT and then decreased, though not falling to baseline levels. In patients who stopped OIT, there was a trend for reversal of these biomarker changes. Higher peanut-IgE and Arah2-IgE at study month 12 were associated with discontinuation. Patient and parent QoL improved from baseline, even in patients who discontinued OIT. **CONCLUSIONS:** Although adjunctive omalizumab allowed for faster and successful desensitization in patients with high peanut-IgE, almost half of patients discontinued OIT within 72 months because of reactions. Patients who stopped therapy had higher month 12 peanut-IgE and Arah2-IgE. It is possible that these patients might benefit from longer omalizumab administration. © 2018 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;7:451-61)

Key words: Oral immunotherapy; Peanut allergy; Omalizumab; Peanut IgE; Peanut IgG4; Desensitization; Arah2; Eosinophilic esophagitis; Follow-up; Long-term

Food allergy is a potentially life-threatening condition affecting up to 6% to 8% of children and 2% to 3% of adults.^{1,2} There is currently no cure for peanut allergy.^{3,4} Oral immunotherapy (OIT) has shown efficacy in studies.⁵⁻¹³ However, long-term outcomes are still not well known. We have reported previously on the first study that evaluated rapid peanut desensitization facilitated by short-term omalizumab treatment, in children with the highest peanut-IgE (median 229 kU/L) reported in peanut OIT trials.¹⁴ Here, we review the clinical outcomes after 6 years of therapy, and report on changes in quality of life (QoL) measures and peanut allergy biomarkers.

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This study was supported by the National Institutes of Health, Clinical and Translational Science Center/Harvard Catalyst (Grant number NIH UL1 RR 025758), the Food Allergy Initiative, the David and Denise Bunning Food Allergy Project Fund, the Jasmine and Paul Mashikian Fund, and the Paul Schimmel and Michelle Franciose Fund.

Conflicts of interest: D. T. Umetsu is an employee at Genentech. L. Schneider receives research support from Regeneron Pharmaceuticals, DBV Technologies, Pfizer, and Genentech; has consulted for Aimmune Therapeutics; and is on the Medical Advisory Board of FARE (Food Allergy Research and Education). R. Rachid received research support from Aimmune Therapeutics and provided consulting services for Aimmune Therapeutics. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication June 2, 2018; revised September 9, 2018; accepted for publication September 13, 2018.

Available online September 26, 2018.

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2213-2198

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<https://doi.org/10.1016/j.jaip.2018.09.015>

Abbreviation used

CoFar- Consortium on Food Allergy Research
 DBPCFC- Double-blind placebo-controlled food challenge
 EoE- Eosinophilic esophagitis
 LTFU- Long-term follow-up
 NSAID- Nonsteroidal anti-inflammatory drug
 OIT- Oral immunotherapy
 PN-IgE- Peanut-specific IgE
 PP- Peanut protein
 QoL- Quality of life
 SPT- Skin prick test

METHODS

This study was approved by the Boston Children's Hospital Institutional Review Board and registered on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01290913) (NCT01290913).

We previously enrolled 13 peanut-allergic patients, 8 to 16 years of age with positive peanut-skin prick test (SPT), peanut-IgE ≥ 20 kU/L, and reactivity to ≤ 50 mg peanut protein (PP) on entry double-blind placebo-controlled food challenge (DBPCFC).¹⁴ Patients received omalizumab for 12 weeks and then ingested incremental doses of PP up to a maximum of 250 mg (cumulative dose 496 mg) administered over 6 hours. Over a median period of 8 weeks, patients returned weekly for up dosing until a daily maintenance dose of 2000 mg PP was reached, at which point omalizumab was discontinued (median week 20, range 19-24 weeks). DBPCFC up to 4000mg PP was performed at week 32, after which patients started consuming 10 to 20 peanuts per day (Figure 1).

After week 52, patients were enrolled in the long-term follow-up (LTFU) study. Patient 4 failed to reach maintenance dosing because of persistent nausea and vomiting, so withdrew at week 15. Patient 7 stopped peanut intake at week 42 after experiencing 2 allergic reactions, but agreed to participate in the LTFU study. The 11 remaining subjects who continued peanut OIT could choose to change peanut dose formulations from available commercial food products. If patients were doing well without reactions, and if their peanut-IgE level was dropping, the protocol included optional spacing from daily to every-other-day for 6 months, then twice a week for 6 months, and finally weekly.

LTFU visits occurred approximately every 6 months, up to 72 months. Subjects were also contacted regularly by telephone and/or email. Allergic reactions were graded using Consortium of Food Allergy Research (CoFar) anaphylaxis criteria.¹³ At baseline and follow-up visits, patients and parents completed validated measures of food allergy QoL and perceived risk of negative food allergy outcomes (detailed in [Supplemental Methods](#) in this article's Online Repository at www.jaci-inpractice.org).

Total IgE, peanut-IgE, and peanut-SPT were measured as previously described.¹⁴ Peanut-specific IgG4, and Arah1 and Arah2 specific-IgG4 and specific-IgE testing was performed by Immuno-Cap at Thermo Fisher Scientific, Phadia US Inc (Portage, MI).

Statistics were calculated using SPSS version 24 (IMB Corporation, Armonk, NY). Wilcoxon signed-rank tests (2-tailed) were used to examine changes in laboratory values in patients at different time points, and QoL and perceived risk of negative food allergy outcomes from baseline to each follow-up visit. The Mann-Whitney *U*-test was used to compare laboratory values across groups. We considered *P* < .05 significant.

RESULTS

Patient outcomes are detailed in [Table 1](#). Of the 12 patients who reached maintenance, 7 continued regular peanut consumption and 5 discontinued OIT (1 before month 12, and 4 during LTFU). Median time to discontinuation for these 5 patients was 39.75 months after study initiation (standard deviation = 19.4 months).

Maintenance dose, frequency, and peanut product changes

Throughout LTFU, some patients changed maintenance frequency, amount, and/or form of peanut. At the start of LTFU, the daily OIT dose was ≥ 2000 mg PP, except for patient 8 who dropped her dose to 1800 mg. Because the optimal maintenance dose has not been determined, dose amounts were decreased when allergic symptoms developed or by patient/family preference. The maintenance dose thus varied between patients from 500 to 3500 mg PP during LTFU (Figure 2, A).

Two patients (2 and 11) opted on regularly spacing their peanut dose. Patient 2, who had concomitant seasonal allergic rhinitis, was gradually spaced to once weekly by month 45. He initially tolerated this well, but experienced 2 allergic reactions at month 48 during peak tree-pollen season, thereafter tolerated every-other-day dosing, and returned to weekly by month 67. Patient 11 has tolerated every-other-day dosing since month 30, except for 1 reaction in month 51 after which she continued every-other-day dosing without issue. Three patients (1, 10, and 12) reported frequently missing or skipping peanut doses from 1 to 3 days per week. Patients 1 and 6 chose to split their dose twice a day, for ease of swallowing peanut capsules and for taste aversion, respectively.

Peanut product used for dosing varied by patient, and also changed over time (Figure 2, B). Seven LTFU participants (54%) had significant aversion to peanut taste and swallowed peanut flour encapsulated into gelatin capsules (approximately 500 mg peanut flour/250 mg PP per capsule). Shifting between products was well tolerated and was not associated with allergic reactions.

Adverse events and outcomes

All LTFU patients reported at least 1 adverse reaction to peanut over the course of the study. Patients who had more adverse events in the first 52 weeks of the study were not the same as those who had more adverse events in LTFU. Through month 72, the 12 subjects experienced a total of 257 adverse reactions ([Table II](#)). Of these, 220 events were grade 1, 37 events were grade 2, and 1 event was grade 3. No subjects required inpatient admission. In total, 29 of 38 grade 2/3 reactions (76%) included respiratory symptoms. The grade 3 reaction and 31% of grade 2 reactions were treated with epinephrine. Five patients had 14 grade 2 events with respiratory symptoms where epinephrine may have been indicated for wheezing. In all of these reactions, symptoms resolved after oral antihistamines and/or inhaled albuterol, without progression of symptoms. Asthma severity (only mild-intermittent or mild-persistent in affected study participants) was not a significant factor in number or severity of reactions.

Six patients experienced a total of 12 reactions requiring epinephrine. Two subsequently discontinued peanut OIT. Patient 5 took approximately 3000 mg PP for 3.5 years before developing hives from peanut at month 46, for which he received epinephrine. He decided to discontinue OIT because

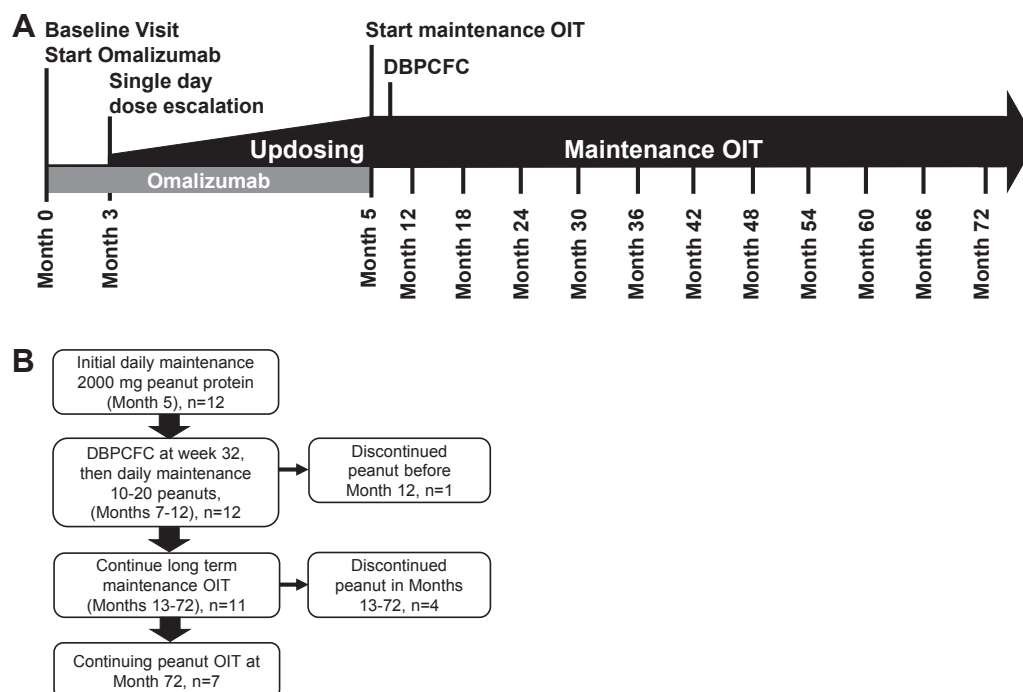


FIGURE 1. Protocol and patient outcomes. **A**, Study timeline. Patients received omalizumab at weeks 0-12, single-day dose escalation at week 12, updosing to 2000 mg PP at weeks 12-20, and were enrolled in LTFU (months 12-72). **B**, Patient outcomes on long-term OIT. Of 13 patients included in the initial study, 12 reached maintenance. Seven continued OIT through month 72; 5 discontinued. *DBPCFC*, Double-blind placebo-controlled food challenge; *LTFU*, long-term follow-up; *OIT*, oral immunotherapy; *PP*, peanut protein.

TABLE I. Characteristics of study patients.

Subject	Age at start (y)	Sex	Maintenance peanut dose (mg PP)		Dose frequency (LTFU end or discontinued)	Outcome at LTFU endpoint	Other atopic conditions
			Start	End			
Patient 1	8	M	3000	3000	Twice daily [†]	Remained on peanut	AR, AS, AD
Patient 2	8	M	2000	1000	Weekly	Remained on peanut	AR
Patient 3	9	F	3500	0	Daily [‡]	Discontinued month 39	None
Patient 4	15	M	0*	0	Daily	Discontinued month 3*	AR, AS
Patient 5	14	M	3000	0	Daily	Discontinued month 46	AR, AS
Patient 6	14	M	2000	500	Twice daily [†]	Remained on peanut	AR, AS
Patient 7	8	M	0	0	Daily	Discontinued month 10	AR
Patient 8	14	F	1800	0	Daily	Discontinued month 21	AR
Patient 9	7	M	2000	2000	Daily	Remained on peanut	AR, AS, AD
Patient 10	10	F	3000	500	Daily	Remained on peanut	AS
Patient 11	11	F	3000	2200	Every other day	Remained on peanut	AR, AD
Patient 12	9	F	3000	1200	Daily	Remained on peanut	AR, AS
Patient 13	8	M	3000	0	Daily	Discontinued month 58	AS

AD, Atopic dermatitis; AR, allergic rhinitis; AS, asthma; *LTFU*, long-term follow-up; *PP*, peanut protein.

Final dose is from month 72 or last report. Patients 3-5, 7, 8, and 13 discontinued peanut before the end of LFTY. Patients 1, 9, 10, and 12 had mild intermittent asthma. Patients 5, 6, and 13 had mild persistent asthma.

*Patient 4 did not reach maintenance or participate in LTFU.

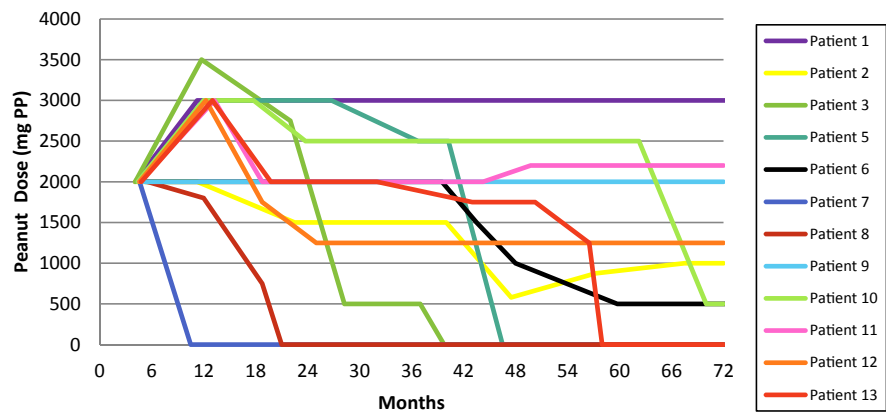
[†]Taken twice daily because of patient preference.

[‡]Exact frequency could not be determined because of patient skipping doses due to reactions.

of that reaction, combined with dose “fatigue” and logistical challenges of avoiding peanut doses with exercise. From months 15 to 22, patient 8 experienced 7 reactions associated with peanut OIT doses, all of which required epinephrine, despite gradually decreasing her dose from 2000 to 750 mg PP. Her

reactions were always associated with factors such as viral illnesses, exercise, menses, or nonsteroidal anti-inflammatory drug (NSAID) administration, and she was very eager to continue on OIT. She finally stopped therapy after her last reaction, which required 2 doses of epinephrine. Four patients

A Peanut Maintenance Dose



B Peanut Products

Subject	Month 5	Month 12	Month 18	Month 24	Month 30	Month 36	Month 42	Month 48	Month 54	Month 60	Month 72
01	F	■	■	■	■	■	■	■	■	■	●
02	F	■ F	■	●	●	●	●	●	●	●	●
03	F	●	●	●	●	●	○	○	○	○	○
05	F	●	■	■	●	●	●	○	○	○	○
06	F	●	■	■	■	■	■	■	■	■	■
07	F	○	○	○	○	○	○	○	○	○	○
08	F	●	●	○	○	○	○	○	○	○	○
09	F	●	■	■	■	■	■	■	■	■	■
10	F	●	■	●	●	●	●	●	●	●	●
11	F	■	■	■	■	■	■	■	■	■	■
12	F	■	■	■	■	■	■	■	■	■	■
13	F	●	●	●	●	●	●	●	●	○	○

F Peanut Flour■ Baked Goods● Capsules

■ Peanut Butter● Peanut Butter Cup● Trail Mix

| ● Roasted Peanuts | ● Unknown Form |
| ○ No peanut | |

■ Peanut M&M's■ PB Sandwich/Crackers

FIGURE 2. Peanut OIT dosing in long-term follow-up. **A**, Maintenance dose for each patient over time. Dose equivalents were calculated in mg PP. **B**, Peanut products used by each subject during the maintenance period. If subjects were taking a combination of peanut dose forms during a given period, multiple types are indicated. *OIT*, Oral immunotherapy; *PP*, peanut protein.

(2, 10, 11, and 12) each required epinephrine for 1 reaction (months 22, 65, 51, and 52, respectively), but continued peanut OIT through month 72. Two patients experienced notable gastrointestinal symptoms leading to peanut discontinuation. From months 22 to 29, patient 3 reported stomachache with no other symptoms, lasting 15 to 120 minutes with most daily peanut doses within 2 hours of

consumption, despite gradually decreasing her dose (3500 to 500 mg). Closer to discontinuation, she started taking her dose more erratically, with abdominal pain occurring only on days when peanut was taken. Her reactions comprised 85% of the grade 1 events for all patients. Patient 13 took 1250 to 3000 mg PP daily for 58 months. Around month 50, he developed occasional vomiting and dysphagia unresolved with antihistamines and

TABLE II. Summary of adverse events by patient during long-term peanut oral immunotherapy months 13-72

Subject	Total reactions per subject	Grade 1	Grade 2	Grade 3	Reactions requiring epinephrine	Associated factors
Patient 1	10	10	0	0	0	None known
Patient 2	5	4	1	0	1	Exercise, seasonal allergies
Patient 3	189	189	0	0	0	One accidental peanut exposure after discontinuing OIT
Patient 5	3	1	2	0	1	Cold weather, missed meal, anxiety, exercise, NSAIDs
Patient 6	7	0	7	0	0	Exercise, missed meal
Patient 7	1	1	0	0	0	Accidental peanut exposure after discontinuing OIT
Patient 8	7	1	6	0	7*	Menses, viral illness, exercise, NSAIDs
Patient 9	1	1	0	0	0	Stopping antihistamines
Patient 10	5	0	5	0	1*	Exercise, missed meal
Patient 11	2	1	0	1	1	Exercise
Patient 12	10	3	8	0	1	Dental abscess, missed meal, exercise, stress, fatigue, viral illness, environmental allergies
Patient 13	17	10	7	0	0	Exercise, viral illness
Total reactions for all subjects	257	220	36	1	12	

LTFU, Long-term follow-up; NSAID, nonsteroidal anti-inflammatory drug; OIT, oral immunotherapy.

Patients 3, 5, 7, 8, and 13 discontinued peanut before the end of LTFU.

Events were graded using the CoFar anaphylaxis scale.¹³

*Patients 8 and 10 required 2 doses of epinephrine for 1 reaction each.

omeprazole. Esophageal biopsy, after 2 months of anti-reflux therapy was consistent with eosinophilic esophagitis (EoE), which prompted peanut discontinuation in month 58. His symptoms resolved after a few weeks, but recurred 5 months later. Repeat endoscopy in month 68 showed ongoing EoE, despite continued peanut avoidance.

Several patients reported common factors associated with adverse reactions (Table E1, available in this article's Online Repository at www.jaci-inpractice.org). Although study patients were advised to avoid exercise for at least 2 hours after consuming peanut, 7 of 12 LTFU patients reported reactions associated with peanut dosing in conjunction with exercise. Heavy exercise associated with competitive sports appeared to be a trigger even after 2 hours of consuming the dose. Other common associations included NSAID use, illness (eg, upper respiratory infections, gastroenteritis), stress/fatigue, seasonal allergy exacerbations, and consuming doses on an empty stomach. Seasonality of reactions also varied. Of 65 nonrecurrent events occurring in specific seasons (which excluded the frequent abdominal pain of patient 3), most occurred in the winter (29 events), compared with 14 in the spring, 11 in the fall, and 11 during summer. Of winter events, 4 were associated with illness, all in 1 patient.

No patients avoided products with peanut precautionary labeling (may contain peanut or processed in a facility with peanut) while on OIT. Although patients were allowed to consume peanut-containing products other than their maintenance dose, none were interested in doing so because of taste aversion.

Peanut allergy biomarkers

At initial study entry, median total IgE for the 12 LTFU subjects was 625.5 kU/L, median peanut-IgE was 259.5 kU/L, and median peanut-SPT wheal was 14 mm (Table E2 and Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). To evaluate the effect of regular peanut consumption on peanut allergy biomarkers, we compared the changes between study start to latest LTFU value for 2 groups: patients continuing peanut OIT through month 72 (n = 7), and

patients who stopped therapy (n = 5, months 43-72 depending on patients).

There was a significant decrease in median peanut-SPT, from 10.5 to 3.5 mm for patients who continued OIT and from 18 to 8.0 mm for patients who discontinued (Table III and Figure E1, available in this article's Online Repository at www.jaci-inpractice.org). Median peanut-IgE significantly decreased from 229 to 4.62 kU/L for patients who continued on OIT, and from 290 to 144 kU/L for those who discontinued. Interestingly, reactions occurred even in some patients with a major decrease in peanut-specific IgE (PN-IgE) (Table E2, available in this article's Online Repository at www.jaci-inpractice.org). For example, patient 10 developed a grade 2 reaction in month 55, despite the large drop in peanut-IgE from 327 kU/L at baseline to 6.14 kU/L at the time of reaction.

Three patients who discontinued peanut showed an initial decrease in peanut-IgE while on OIT, followed by a rise after discontinuing peanut (Figure 3, A). Interestingly, patient 8 (who developed recurrent anaphylactic reactions) and patient 13 (who developed EoE) instead had a continued decrease in peanut-IgE after discontinuing peanut. There was additionally a significant decrease in total IgE in both groups. The peanut-IgE:total IgE ratio (Figure 3, B) was significantly decreased at the study end only in patients who continued on OIT.

Peanut-IgG4 peaked at first, and then decreased for all OIT patients (Figure 3, C). Decreasing peanut dose did not appear to correlate temporally with decreasing peanut-IgG4. Nevertheless, peanut-IgG4 increased significantly from the study start to end for patients who continued peanut OIT, whereas the change was not significant for those who discontinued peanut. The peanut-IgE:peanut-IgG4 ratio decreased for all patients; however, changes were only significant in the continuing group. In patients who stopped peanut, the peanut-IgE:peanut-IgG4 ratio trended upward after discontinuation (Figure 3, D).

Patients who continued peanut had a significant persistent decrease in peanut Arah1-IgE and Arah2-IgE from baseline to latest value (Table III, Figure 4, A and B). In contrast,

TABLE III. Comparison of peanut and food allergy biomarkers in long-term follow-up patients

Biomarker	Continuing peanut OIT patient group					Discontinued peanut patient group					Discontinued vs continuing patient groups		
	Entry median	Month 12 median	Latest median	Trend vs start	P value latest vs start	Entry median	Month 12 median	Latest median	Trend vs start	P value latest vs start	At entry, P value	Month 12, P value	At latest, P value
Total IgE (ku/L)	630	282	103	↓*	0.028*	621	969	453	↓*	0.043*	NS	NS	0.030*#
Peanut IgE (ku/L)	229	42.9	4.62	↓*	0.018*	290	92.5	144	↓*	0.043*	NS	0.030*#	0.010*#
Peanut SPT (wheal in mm)	10.5	6	3.5	↓*	0.018*	18	6.25	8	↓*	0.043*	NS	NS	NS
PN-IgE:IgE ratio (kU/L:kU/L)	0.24	0.14	0.04	↓*	0.018*	0.45	0.11	0.28	↓	NS	NS	NS	0.030*#
Peanut IgG4 (mg/mL)	0.13	21.3	9.49	↑*	0.018*	0.39	25.75	3.27	↑	NS	NS	NS	NS
Peanut IgE:peanut IgG4 ratio (mg/L:mg/L)	1.07	0.005	0.002	↓*	0.018*	1.1	0.0253	0.0835	↓	NS	NS	NS	0.006*#
Ara h 1 IgE (kU/L)	10.3	7.92	0.7	↓*	0.018*	13.6	34.7	11.91	↓	NS	NS	NS	0.038*#
Ara h 2 IgE (kU/L)	25.1	19.1	1.35	↓*	0.018*	49	45.45	25.7	↓	NS	NS	0.012*#	0.024*#
Ara h 1 IgG4 (mg/L)	0.07	1.06	0.79	↑*	0.028*	0.11	3.51	0.125	↑	NS	NS	NS	NS
Ara h 2 IgG4 (mg/L)	0.07	10	6.33	↑*	0.018*	0.07	17.2	2.45	↑	NS	NS	NS	NS
Arah1-IgE:Arah1-IgG4 ratio (mg/L:mg/L)	0.329	0.0137	0.0021	↓*	0.018*	0.39	0.0426	0.0989	↓	NS	NS	NS	NS
Arah2-IgE:Arah2-IgG4 ratio (mg/L:mg/L)	0.32	0.0026	0.0011	↓*	0.018*	1.6	0.0083	0.0187	↓	NS	NS	NS	NS

LTFU, Long-term follow-up; OIT, oral immunotherapy.

Median biomarker values were calculated at study entry, month 12 (start of LTFU), and latest available LTFU time point (months 42-73), for patients continuing OIT and those who discontinued. Comparisons of patients at study entry vs latest available LTFU time point were calculated by the Wilcoxon signed-rank test. Arrows indicate the trend at latest time point vs study start. #: median values higher in patients who discontinued than those continuing OIT. * $P < .05$; ** $P < .01$; NS: P value not significant.

Arah1-IgG4 and Arah2-IgG4 followed similar trends to total peanut-IgG4, showing an initial increase followed by a drop in all patients (Figure 4, C and D). An increase in Arah1-IgG4 and Arah2-IgG4 from baseline to latest value was significant only in the group continuing OIT. The Arah1-IgE:Arah1-IgG4 and Arah2-IgE:Arah2-IgG4 ratios decreased from start to latest in both groups (Figure 4, E; and Figure E2, available in this article's Online Repository at www.jaci-inpractice.org), but only significantly in the group continuing OIT.

We also compared biomarkers in the patients continuing peanut with those who discontinued (Table III and Table E3, available in this article's Online Repository at www.jaci-inpractice.org). At the start of LTFU (study month 12), peanut-IgE and Ara-h2-IgE were significantly higher in patients who later discontinued peanut. Discontinued patients also had significantly higher total IgE ($P = .03$), peanut-IgE ($P = .010$), peanut-IgE:IgE-ratio ($P = .030$), peanut-IgE:IgG4-ratio ($P = .008$), Arah1-IgE ($P = .038$), and Arah2-IgE ($P = .024$) at the latest follow-up, compared with patients who continued.

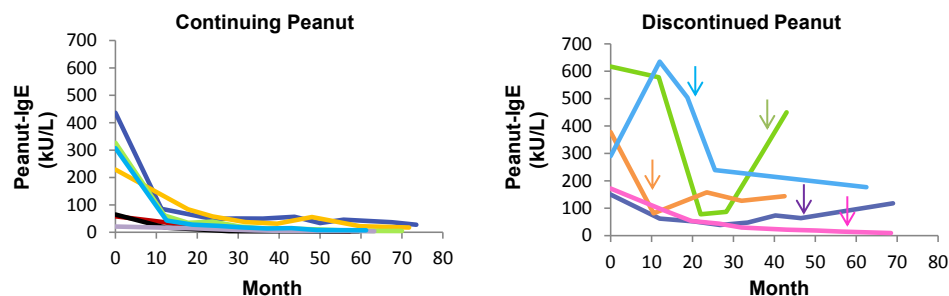
Quality of life

Both patient and parent QoL demonstrated significant improvement from baseline at each study time point (Table IV). Child ratings of the perceived risk of having a severe reaction if peanut was accidentally ingested were significantly reduced from baseline at each study time point, and ratings of the perceived risk of dying were significantly reduced from baseline to all but one time point (month 24). To determine whether improvement in QoL scores was distributed across all items or due to changes on specific items, we examined change on individual item ratings between baseline and the most recent visit completed for each participant (Table E4, available in this article's Online Repository at www.jaci-inpractice.org). Patient ratings demonstrated statistically significant improvement for all but one of 17 items (disappointment when people don't take your food allergy into account). Parent ratings of their own QoL demonstrated statistically significant improvement for all items (Table E5, available in this article's Online Repository at www.jaci-inpractice.org). All patients demonstrated improvement in their QoL score at their most recent study visit compared with baseline, including those who had discontinued peanut, with a significant decrease (improvement) in median QoL scores from 3.4 to 0.2 for those who continued on peanut ($P = .028$) and from 4.5 to 1.8 for those who had discontinued peanut ($P = .043$).

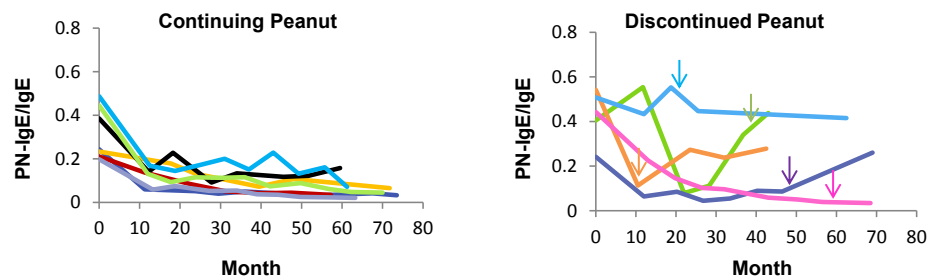
DISCUSSION

Although OIT trials have shown efficacy in terms of desensitization in up to 80% of patients,^{6,7,10,13,19} LTFU studies have been scarce, and when performed, have shown variable results.²⁰⁻²⁴ As OIT may modify disease but does not result in cure, it is critical to evaluate its long-term outcomes. Here, we report on one of the longest follow-up studies to date, evaluating OIT initially facilitated with omalizumab, in 13 highly sensitive patients reacting to traces of PP (≤ 50 mg) on entry DBPCFC, with the highest entry median peanut-IgE (229 kU/L) yet reported in peanut OIT trials. After up to 72 months of therapy and up to 67 months of maintenance, only 7 of the 13 initially enrolled¹⁴ patients (54%) continued on peanut OIT. Hence, although omalizumab allowed for faster and effective desensitization in these very sensitive patients, 46% discontinued therapy. Subjects experienced allergic reactions to peanut during LTFU

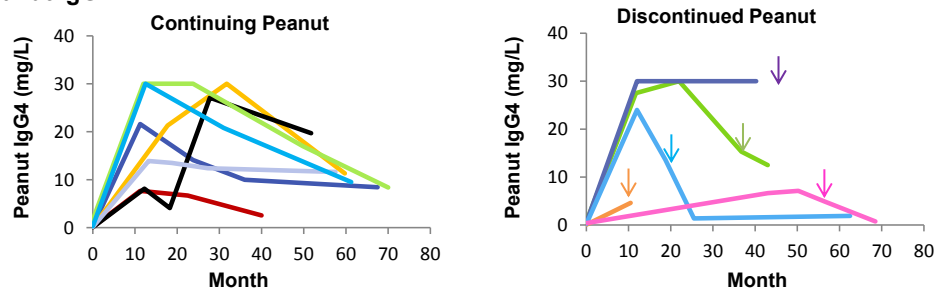
A Peanut-specific IgE



B Peanut-Specific IgE: Total IgE Ratio



C Peanut IgG4



D Peanut IgE: Peanut IgG4

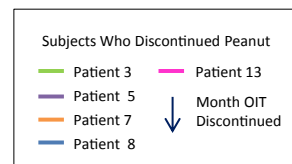
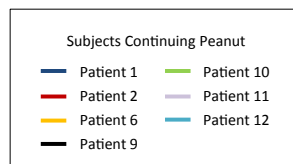
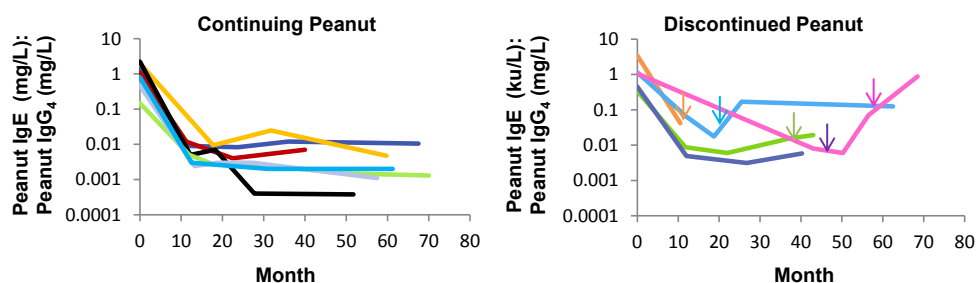


FIGURE 3. Measurement of peanut-IgE (A), peanut-IgE:IgE (B), peanut-IgG4 (C), and peanut-IgE:peanut-IgG4 (D) in patients throughout LTFU. Groups include the 7 patients who continued OIT (left) and 5 patients who discontinued (right). Arrows (color-coded by patient) indicate month of OIT discontinuation. Patient 5 discontinued after last peanut-IgG4 measurement was obtained (month 46). *LTFU*, Long-term follow-up; *OIT*, oral immunotherapy.

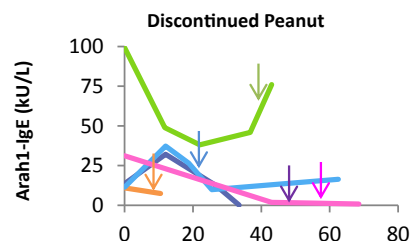
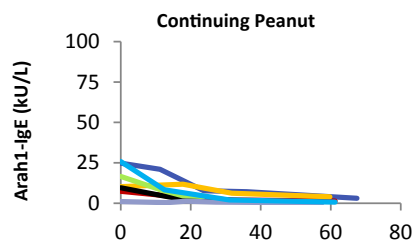
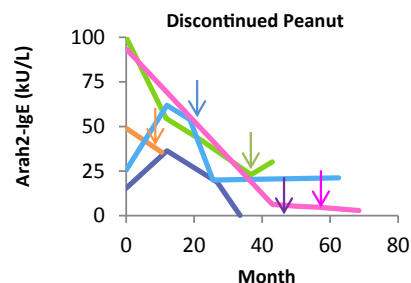
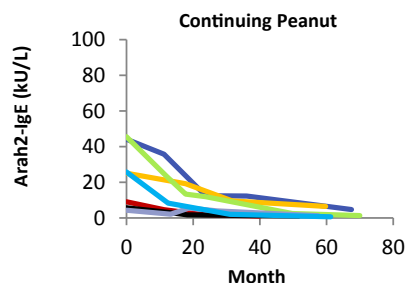
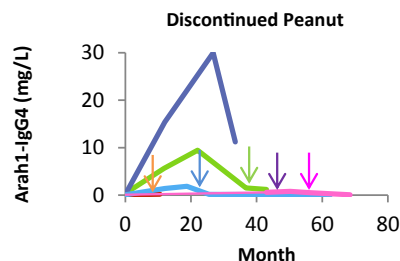
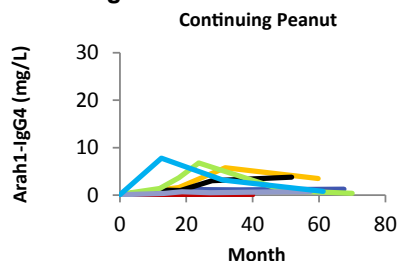
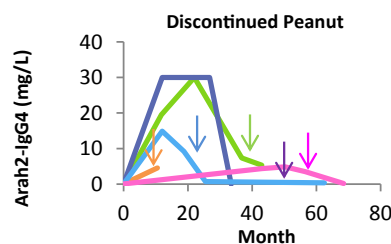
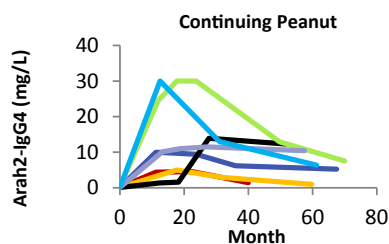
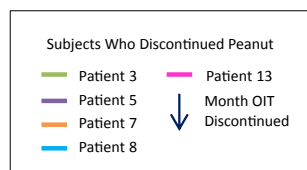
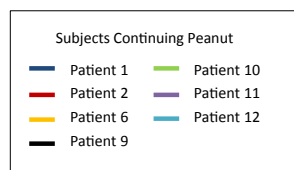
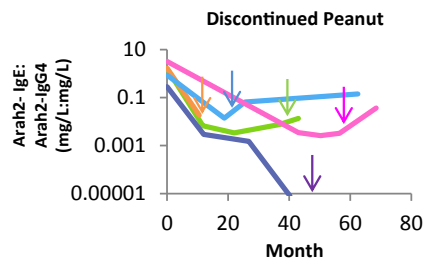
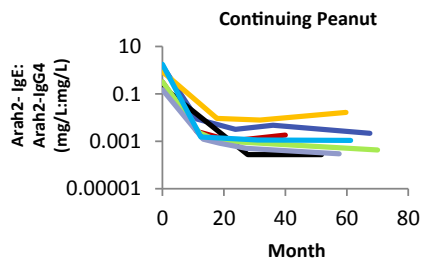
A Ara h 1 IgE**B Ara h 2 IgE****C Ara h 1 IgG4****D Ara h 2 IgG4****E Ara h 2-IgE: Ara h 2-IgG4**

FIGURE 4. Peanut component IgE and IgG4 during the LTFU study. Ara h 1-IgE (A), Ara h 2-IgE (B), Ara h 1-IgG4 (C), Ara h 2-IgG4 (D), and the peanut Ara h 2-IgE:peanut Ara h 2-IgG4 (E) ratio are grouped by patients continuing peanut OIT through month 72 (left) and patients who discontinued (right). Arrows (color-coded by patient) indicate month in which OIT was discontinued. Patient 5 discontinued after last peanut measurements were obtained (month 46). LTFU, Long-term follow-up; OIT, oral immunotherapy.

TABLE IV. Change in QoL and perceived risk scores for patients and parents

Outcome measure	Visit					
	Baseline Median (N)	12 mo Median (N)	24 mo Median (N)	36 mo Median (N)	48 mo Median (N)	60 mo Median (N)
Patient QoL	4.5 (11)	0.4 (12)**	0.8 (12)**	0.6 (12)**	0.3 (10)**	0.3 (10)**
Parent QoL	2.5 (12)	1.2 (12)**	0.9 (12)**	1.0 (12)**	0.8 (10)**	1.0 (9)**
Patient perceived risk—severe reaction	4.0 (11)	1.0 (12)**	1.0 (12)**	1.0 (12)**	1.0 (10)**	1.0 (10)*
Patient perceived risk—death	1.0 (10)	0.0 (12)*	1.0 (12)	0.0 (12)*	1.0 (10)*	0.5 (10)*

QoL, Quality of life.

QoL and perceived risk scores range from 0 to 6, with higher scores indicating a greater negative impact on QoL/greater perceived risk.¹⁵⁻¹⁸ P values represent change from baseline to follow-up score. * $P < .05$, ** $P < .01$.

even after years of therapy, and despite some patients' very significant drops in peanut-IgE. Every patient experienced a dose-related reaction, and 54% had reactions treated with epinephrine. In another LTFU peanut OIT study of patients with lower initial median PN-IgE (85.4 kU/L), only 25 of 39 (64%) patients remained on peanut OIT at 5 years, and 7 withdrew because of allergic reactions.^{6,24} Only 31% of patients on milk OIT were tolerating full servings of milk with minimal or no symptoms during follow-up.⁹

Reaction rates in our study might have been partly related to relatively higher maintenance doses. Optimal peanut OIT maintenance doses to balance protection from accidental exposure against risk of reaction to OIT dosing, and whether and when doses can be tapered, remain to be determined. In another LTFU study, patients consuming either high or low doses (median 300 mg) of multiple (up to 8) food OIT with and without omalizumab, for up to 62 months of maintenance therapy, had no anaphylactic reactions.²⁵ By that study's end, all but 2 patients were on low-dose maintenance. In another long-term outcome of multiple OIT without omalizumab, there was no anaphylaxis up to 72 months of maintenance²⁰ and there were no differences in adverse events between the high-dose (2000-4000 mg) and low-dose maintenance (300 mg). However, in preliminary results of a phase II peanut OIT trial, higher doses appeared to be associated with a higher rate of allergic reaction, though peanut-IgE declined faster than when lower doses (300 mg) were administered.²⁶ Currently, large-scale phase III trials are evaluating safety and efficacy of 300 mg PP maintenance doses (NCT02635776 and NCT03126227). Some of our patients might conceivably have better tolerated peanut OIT if tapered to lower doses at an appropriate time.

The benefit of combining omalizumab with OIT requires further evaluation. We and others have shown that the use of omalizumab during OIT is associated with decreased frequency and severity of reactions.^{14,27,28} Prior studies have shown that patients with elevated food specific-IgE are more prone to failing OIT.^{19,29,30} Our patients had the highest median peanut-IgE reported so far in any peanut desensitization trial, as most other studies reported median peanut-IgE <100 kU/L,^{19,22,29} suggesting that patients with high food specific IgE might better tolerate the initial desensitization if treated with omalizumab. Indeed, all 12 patients enrolled in the LTFU were initially successfully desensitized when treated in combination with omalizumab. At baseline, peanut-IgE and Arah2-IgE level were not predictors of discontinuation at any time. However at study month 12 (approximately 7 months after reaching maintenance

and stopping omalizumab), peanut-IgE and Arah2-IgE were significantly higher in the discontinued group. Although these observations arise from a small number of patients, they suggest that elevated peanut-IgE and Arah2-IgE early in OIT could be helpful in identifying patients, who are at a greater risk of recurrent reactions after stopping omalizumab, and who are presumably more resistant to desensitization. It is possible that such patients might benefit from more prolonged adjunctive therapy with anti-IgE. It is also conceivable that these patients could also have benefited from a slower desensitization as the long-term value and efficacy of rapid desensitization requires further evaluation. In addition, omalizumab alone has been shown to increase the threshold of reactivity to peanut during food challenges,³¹ suggesting that long-term omalizumab monotherapy without the additional risk of OIT may be valuable in some patients with food allergy.

We also observed seasonal variation in reported adverse events with more reactions in the wintertime, as well as association with seasonal allergy symptoms. Geographical location might have also played a role in the outcome. Higher rates of emergency department visits for acute food allergy reactions have been observed in the northeastern USA compared with southern regions.³²

The effect of dose spacing (ie, dose tapering schedule) on allergic reactions requires further evaluation. Of 5 patients in this study regularly or frequently taking peanut doses less than daily, 4 patients experienced dose-related reactions. It is possible that these patients could have benefitted from consistent daily dosing though we could not evaluate this further considering the small number of patients. Although decreasing the frequency of maintenance dosing may help patients with significant taste aversion or dose-ingestion "fatigue," potential issues with this approach include noncompliance because of forgetfulness. Dose spacing might have to be re-adjusted during allergy seasons, or perhaps instituted after some combination of laboratory and clinical markers indicate an appropriate reduction in allergic responsiveness. Larger studies are currently being conducted to evaluate the effect of spacing on adverse reactions, albeit with much lower maintenance doses (NCT02993107).

Recurrent abdominal symptoms were noted in 3 of 13 patients originally enrolled. Patient 3 developed abdominal pain occurring shortly after taking her peanut dose. Symptoms did not occur on days when peanut was not consumed and were suggestive of immediate hypersensitivity reactions. On the other hand, patient 4 exhibited during up dosing abdominal pain and hypersalivation not immediately related to peanut dosing. Patient 13 reported episodes of dysphagia from month 53 and was diagnosed with EoE at month 58. As EoE persisted after peanut

interruption, peanut OIT cannot be confirmed as the sole cause of his EoE. Peanut might have played a role, because avoidance led to resolution of symptoms for several months. In a few patients in other studies, EoE has developed later in OIT, with or without omalizumab therapy.^{33,34} This highlights the importance of LTFU for OIT patients, to monitor not only for IgE-mediated reactions, but also for EoE manifestations.

During LTFU, all patients tried different forms of peanut products. None reacted on switching products. At various times, 7 patients tried swallowing encapsulated peanut flour because of significant taste aversion; doses were as tolerated as other peanut forms. Larger studies are needed to evaluate the safety of the use of encapsulated peanut flour in OIT maintenance therapy.

Consistent with reports of previous OIT protocols up to 5 years from start to latest follow-up,^{6,20-24} our patients exhibited decreased PN-IgE (including Arah1-IgE and Arah2-IgE), peanut SPT, total IgE, peanut-IgE:total-IgE ratio, and peanut-IgE:peanut-IgG4 ratio. The Arah1-IgE:Arah1-IgG4 and Arah2-IgE:Arah2-IgG4 ratios, to our knowledge not previously reported, decreased during LTFU, significantly so in patients continuing OIT. For peanut-IgG4, Arah1-IgG4, and Arah2-IgG4, we also observed a corresponding increase on OIT, peaking in the first 1 to 2 years, followed by a decrease, though final values were ultimately significantly higher at the study end than at the study initiation. This contrasts with findings from other studies, which have reported increased peanut-IgG4 after 12 to 60 months of peanut OIT.^{21,23,24} In patients who discontinued OIT, there was a trend for reversal of these biomarker changes. Three patients showed a rise in peanut-IgE after discontinuing peanut, though peanut-IgE levels did not return to pre-OIT baseline. Two other patients (8 and 13) had significant adverse reactions while on OIT (recurrent anaphylaxis and EoE, respectively) and, interestingly, exhibited decreased peanut-IgE after peanut discontinuation. Patient 8 had a persistent increase in her PN-IgE up to 504 kU/L at the time of her last allergic reaction (month 20). After stopping OIT, her peanut-IgE dropped to 239 kU/L in month 25, then 117 kU/L at month 62, suggesting a positive feedback inflammatory loop while on OIT. Patient 13 had an entry peanut-IgE of 172 kU/L. His level dropped from 18.8 to 14.8 kU/L in months 50-56, the period during which he started experiencing EoE symptoms. Repeat peanut-IgE was 9.4 kU/L in month 68, approximately 10 months after peanut discontinuation. Patients who discontinued also had significantly higher total IgE, peanut-IgE, peanut-IgE:IgE-ratio, and peanut-IgE:peanut-IgG4 ratio, at the latest follow-up. We have recently reported that after 2 years of therapy, OIT supplemented with omalizumab suppressed the Th2 cell-like phenotype of peanut-specific Treg cells and restored their function, an effect that could be recapitulated *in vitro* by the blockade of IL-4 receptor signaling in Treg cells.³⁵ Larger long-term studies are needed to further evaluate these immunoglobulin and Treg biomarker levels, as well as basophil activation while on OIT and after discontinuation.

Prior studies have shown that sustained unresponsiveness after 4 weeks of food interruption can only be achieved in 50% of patients who received OIT for up to 4 to 5 years, primarily in patients whose baseline peanut-IgE levels were low.^{24,36} Considering these outcomes, and that our patients experienced allergic reactions despite several years of therapy, we decided to postpone the evaluation of sustained unresponsiveness.

QoL improvement was observed in patients who continued peanut throughout LTFU, and also in those who discontinued peanut OIT, even after stopping peanut. Patients and their parents also reported reduced expectations of severe reactions and death from accidental peanut, which may alleviate allergy-related anxiety.

The clinical applicability to OIT alone or combined with omalizumab in food-allergic patients in the "real world," not just in highly motivated patients in an intensive research setting, remains to be determined. Logistical challenges include persistent risk of allergic reaction despite years of therapy, taste aversion, dose fatigue, and lifestyle limitations related to dose administration. Nonetheless, all study patients reported improved QoL. To evaluate the long-term value of these therapeutic interventions, larger, multicenter, long-term prospective studies are needed to compare the outcome of peanut OIT with and without omalizumab, with a third cohort of patients avoiding peanut. Of particular interest are patients with persistently elevated peanut-IgE and Arah2-IgE earlier in OIT, as these appear to be more resistant to long-term maintenance OIT. It is possible that these patients might benefit from longer omalizumab therapy, slower desensitization, or anti-IgE monotherapy. The optimal duration of omalizumab therapy if any in such patients still remains to be determined.

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ONLINE REPOSITORY SUPPLEMENTAL METHODS

QoL assessment

Patient QoL. Patients aged 7 to 12 years at baseline completed the Food Allergy Quality of Life Questionnaire-Child Form (FAQLQ-CF)^{E1} and those aged 13-17 years at baseline completed the Food Allergy Quality of Life Questionnaire-Teen Form (FAQLQ-TF).^{E2} Items address the impact of allergen avoidance, dietary restriction, risk of accidental exposure, and emotional burden on quality of life. Given the study's small sample size, 17 questions common across both age-versions of the questionnaire were used to combine data across all study participants. Items were rated on a 7-point Likert scale (0 = not troubled to 6 = extremely troubled) and averaged for a total score. Internal consistency for this 17-item measure was good (Chronbach's $\alpha = 0.95$).

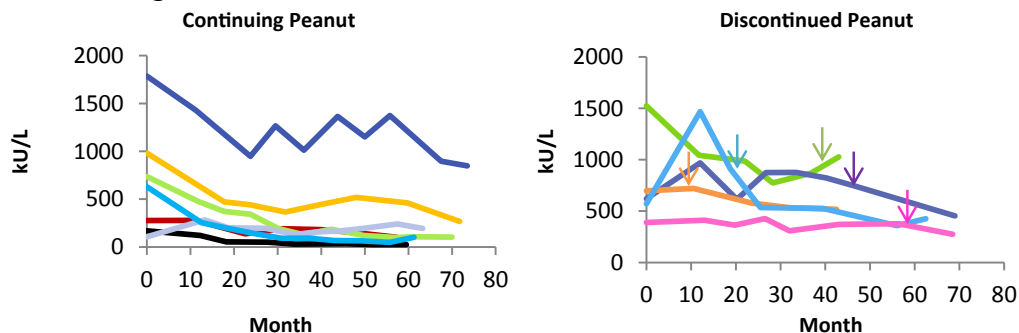
Parent QoL. Parents completed the 17-item Food Allergy Quality of Life-Parental Burden Questionnaire (FAQL-PB).^{E3} Items assess the impact of food allergy on parental quality of life,

such as limitations on social activities, anxiety, concerns about leaving the child in the care of others, frustration, and sadness. Items were rated on a 7-point Likert scale (0 = not limited/troubled to 6 = extremely limited/troubled) and averaged for a total score.

Patient perceived risk of negative food allergy outcomes. Patients completed 2 questions from the validated Food Allergy Independent Measure (FAIM^{E4}), a self-report instrument that reflects the patient's perceived food allergy-related risk. Questions completed for this study included the perceived expectation of a severe reaction or death following an accidental exposure. Perceived risk was rated on a 7-point Likert scale (0 = 0% chance to 6 = 100% chance).

Experience with peanut consumption. Patients and parents were asked questions about peanut consumption at follow-up visits, including information about peanut form and dose, as well as open-ended questions about barriers to peanut consumption (eg, taste/texture, anxiety, tired of taking dose).

A Total IgE



B Peanut Skin Prick Test

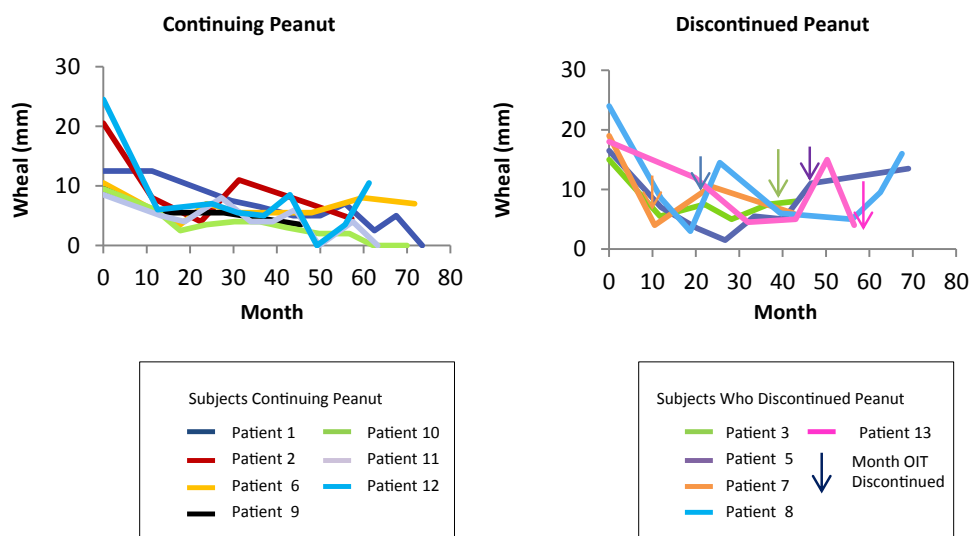


FIGURE E1. Total IgE (A) and peanut skin prick testing (SPT) (B) in study patients throughout long-term follow-up. Groups include the 7 patients who continued peanut OIT (left) and 5 patients who discontinued (right). Arrows (color-coded by patient) indicate month in which OIT was discontinued. *OIT*, Oral immunotherapy.

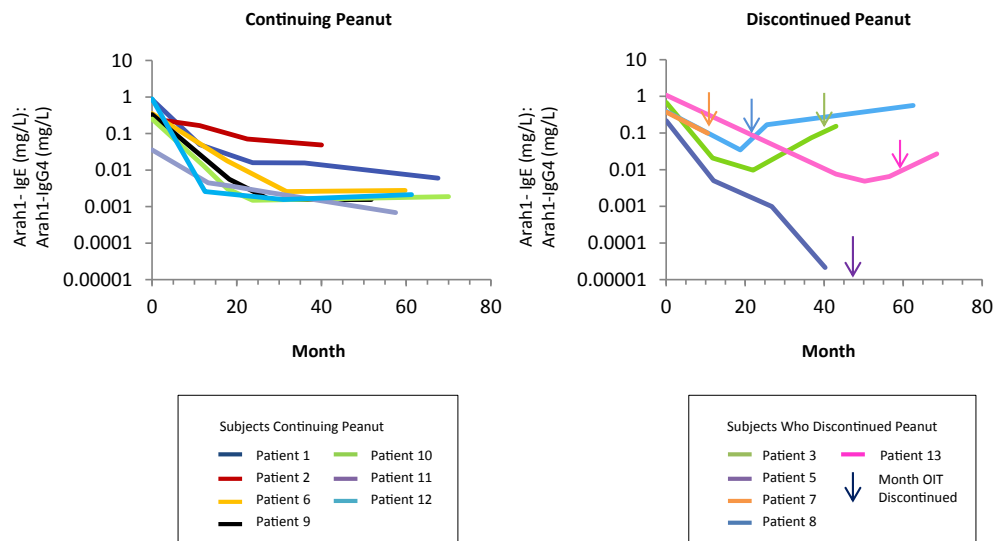
Arah1-IgE:Arah1-IgG4 ratio

FIGURE E2. Peanut Arah-IgE:Arah1-IgG4 ratio in long-term peanut OIT patients over time. Peanut Arah1-IgE and Arah1-IgG4 were measured at study entry and during the study at selected time points. Groups include the 7 patients who continued peanut OIT (left) and 5 patients who discontinued (right). Arrows (color-coded by patient) indicate month in which OIT was discontinued. *OIT*, Oral immunotherapy.

TABLE E1. Summary of factors associated with adverse events during long-term peanut oral immunotherapy

Associated factors	No. of events	No. of patients
Exercise	18	7
Illness	8	3
Stress	6	2
Menses	1	1
Seasonal allergies	3	2
Empty stomach/missed meal	8	4
NSAID	3	2
Exposure to cold/hot environment	2 (cold)/1 (hot)	2 (cold)/1 (hot)
Accidental exposure	2	2
Seasonality	Total events by season	Events associated with illness
Winter	29	4 (1 patient)
Summer	11	0
Spring	14	1
Fall	11	3 (1 patient)
Severity (CoFar grade)	Total events	No. of patients
Grade 1	220	10
Grade 2	36	7
Grade 3	1	1

CoFar, Consortium of Food Allergy Research; *NSAID*, nonsteroidal anti-inflammatory drug.

Seasonality was recorded for isolated (nonrecurring) events for which a specific month or time of year was reported.

TABLE E2. Peanut allergy biomarkers in long-term follow-up peanut OIT patients

Subject	Latest month	Total IgE (kU/L)		Peanut IgE (kU/L)		Peanut SPT wheal (mm)		Peanut IgG4 (mg/L)		Ara h 1 IgE (kU/L)		Ara h 2 IgE (kU/L)		Ara h 1 IgG4 (mg/L)		Ara h 2 IgG4 (mg/L)	
		Entry	Latest	Entry	Latest	Entry	Latest	Entry	Latest	Entry	Latest	Entry	Latest	Entry	Latest	Entry	Latest
Patient 1	73	1786	847	436	27.8	12.5	0	0.17	8.43	24.8	3.13	44.2	4.73	<0.07	1.25	<0.07	5.24
Patient 2	57	276	101	58.2	3.45	20.5	4.5	0.13	2.56	7.4	1.42	9.13	1.07	<0.07	<0.07	<0.07	1.41
Patient 3	43	1524	1027	617	450	15	8	0.7	12.5	99.3	76	>100	30.2	0.35	1.19	0.15	5.33
Patient 4	4	485	1034	84	592	18	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Patient 5	69	621	453	150	118	16.5	13.5	0.53	>30*	13.6	<0.10*	15.4	<0.10*	0.15	11.2*	0.13	>30.0*
Patient 6	71	981	267	229	17.4	10.5	7	0.12	11.3	10.3	4.04	25.1	6.51	<0.07	3.49	<0.07	0.95
Patient 7	42	698	518	378	144	19	6	<0.07	4.63	10.9	7.42	49	35.5	<0.07	0.18	<0.07	4.55
Patient 8	62	571	426	290	177	24	9.5	0.21	1.91	11.4	16.4	25.5	21.2	<0.07	<0.07	<0.07	0.36
Patient 9	59	169	26	65.1	4.1	9.5	3.5	<0.07	19.7	9.62	0.64	5.77	1.21	<0.07	3.78	<0.07	12.3
Patient 10	70	735	103	327	4.6	9.5	0	1.62	8.38	16.6	0.29	45.6	1.35	0.16	0.37	0.34	7.53
Patient 11	63	106	194	21	4	8.5	0	0.11	11.6	1.04	0.22	4.36	1.29	<0.07	0.77	<0.07	10.4
Patient 12	61	630	102	307	7.27	24.5	10.5	0.29	9.49	25.8	0.7	51.4	2.87	<0.07	0.79	<0.07	6.33
Patient 13	68	389	274	172	9.4	18	4	0.39	0.75	31.2	0.79	93.5	2.91	<0.07	<0.07	<0.07	0.19

LFTU, Long-term follow-up; *OIT*, oral immunotherapy.

Patients 3-5, 7, 8, and 13 discontinued peanut before the end of LTFU.

*Data obtained before discontinuing OIT.

TABLE E3. Peanut allergy biomarkers in long-term follow-up peanut OIT patients at 12 months

Subject	Total IgE (kU/L)	Peanut IgE (kU/L)	Peanut SPT wheal (mm)	Peanut IgG4 (mg/L)	Ara h 1 IgE (kU/L)	Ara h 2 IgE (kU/L)	Ara h 1 IgG4 (mg/L)	Ara h 2 IgG4 (mg/L)
1	1429	85.7	12.5	21.6	21	35.8	1.01	10
2	278	38.2	8	7.66	4.81	4.69	0.07	4.38
3	1043	578	5.5	27.5	48.9	54.5	5.63	19.5
4	ND	ND	ND	ND	ND	ND	ND	ND
5	969	62.1	7	30	32.1	36.4	15.4	30
6	471	84.1	3.5	21.3	11.8	19.2	1.59	5.02
7	720	81.4	4	4.63	7.42	35.5	0.18	4.55
8	1467	635	8.5	24	37.3	61.9	1.39	14.9
9	121	17	5.5	8.11	4.5	3.17	1.06	1.36
10	471	61.7	6	30	7.92	23.4	1.39	24.6
11	282	16.7	5	13.9	1.3	5.61	0.77	11
12	255	42.9	6	30	8.35	19.1	7.79	30
13	411	ND	ND	ND	ND	ND	ND	ND

LTFU, Long-term follow-up; OIT, oral immunotherapy.

Patients 3-5, 7, 8, and 13 discontinued peanut before the end of LTFU.

TABLE E4. Change in patient QoL items from baseline to the most recent follow-up visit

Item	Median change
How troublesome do you find it because of your food allergy that...	
Must always watch what you eat	-3.0**
Can eat fewer things/products	-2.0**
Are limited in buying things you like	-2.0**
Have to read labels	-4.0**
Have to refuse food when you do things with others	-2.0*
Can less easily accept invitation to stay for a meal	-1.0*
Can taste or try fewer things when eating out	-2.0**
Have to check whether you can eat something when eating out	-3.0**
Hesitate eating certain foods when you don't know if it is safe	-3.0**
Must be careful about touching certain foods	-3.0**
The ingredients of a product change	-3.0**
The label states "may contain traces of ..."	-3.0**
You have to explain food allergy to people around you	-3.0*
Others eat the food you are allergic to when you do things with others	-3.0**
How frightened are you..	
Of an allergic reaction	-3.0**
Of eating the wrong food by accident	-3.0**
To eat something you have never eaten before	-2.0*
How disappointed are you...	
When people don't take your food allergy into account	-1.0

QoL, Quality of life.

Items rated on the 0-6 scale; negative scores indicate improvement in quality of life. * $P < .05$, ** $P < .01$.

TABLE E5. Change in parent QoL items from baseline to the most recent follow-up visit

Item	Median change
How limited is your... by your child's food allergy	
Choice of vacation	−1.5*
Choice of restaurant	−1.0**
Ability to participate in social activities	−2.0*
In the past week, how troubled have you been by/that	
The need to spend extra time preparing meals due to food allergy	−1.0**
The need to take special precautions before going out of the home	−1.0**
Anxiety relating to food allergy	−1.0*
The child may not overcome food allergy	−1.0*
Possibility of/actually leaving child in care of others	−1.0**
Others' lack of appreciation for seriousness of food allergy	−1.0*
Sadness regarding burden child carries because of food allergy	−2.5**
Child attending school, camp, daycare because of food allergy	−1.0**
Concerns for child's health because of food allergy	−1.0**
Worry you will not be able to help child if they have allergic reaction	−0.5*
Worry child will not have a normal upbringing because of food allergy	−1.0*
Concerns for child's nutrition because of food allergy	−1.0*
Issues concerning child being near others when eating	−1.0**
Being frightened by thought that child will have a reaction	−1.0**

QoL, Quality of life.

Items rated on the 0-6 scale; Negative scores indicate improvement in quality of life. * $P < .05$, ** $P < .01$.**REFERENCES**

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