Original Article

First Real-World Effectiveness Analysis of Preschool Peanut Oral Immunotherapy

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What is already known about this topic? Preschool peanut oral immunotherapy in a real-world setting has been shown to be safe; 0.4% of patients experienced a severe reaction, and 4.1% received epinephrine, during build-up.

What does this article add to our current knowledge? About 78.6% of preschoolers on peanut oral immunotherapy maintenance for 1 year had a negative cumulative 4000-mg oral food challenge without symptoms, and 98.3% could tolerate greater than or equal to *1000 mg, sufficient to protect against accidental exposures.*

How does this study impact current management guidelines? Real-world peanut oral immunotherapy is effective in preschoolers who received the follow-up oral food challenge and should be considered as an alternative to current recommendations to avoid peanut.

BACKGROUND: We previously described safety of preschool peanut oral immunotherapy (P-OIT) in a real-world setting; 0.4% of patients experienced a severe reaction, and 4.1% received epinephrine, during build-up.
OBJECTIVE: To determine the effectiveness of preschool P-OIT after 1 year of maintenance.
METHODS: Preschoolers (9-70 months) with at least 1 objective reaction to peanut (during baseline oral food challenge (OFC) or P-OIT build-up) received a follow-up OFC to cumulative 4000 mg protein after 1 year on 300 mg peanut daily maintenance. Effectiveness of desensitization was defined as proportion of patients with a negative follow-up OFC. Symptoms and treatment at follow-up OFC were recorded.
RESULTS: Of the 117 patients who successfully completed 1 year of P-OIT and subsequently underwent a cumulative 4000-mg follow-up OFC, 92 (78.6%) had a negative OFC and 115

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Conflicts of Interest: L. Soller participates in research sponsored by DBV Technologies. E. M. Abrams is a member of the Scientific Advisory Board for Food Allergy Canada. S. Kapur has received speaking honorarium from Pediapharm and has been a member of advisory boards for ALK, Bosch Health, Mylan, Pediapharm, and Pfizer. M. McHenry has received a speaking honorarium from Merck and has been on an advisory committee for Novartis. T. K. V. Leek has served on advisory boards for Aralez and Pediapharm, and has served on speaker bureaus for and received honoraria from Aralez, Pediapharm, and Pfizer. J. Yeung has received unrestricted educational grants from AstraZeneca, Stallergenes Greer, Novartis, Sanofi, Pediapharm, and Covis Pharma and has been on the following advisory committees: Pfizer, Health Link BC, Stallergenes Greer, Sanofi, and LEO Pharma. T. Wong has received speaking honoraria from Stallergenes Greer, Novartis, and Pfizer and is a subinvestigator in research sponsored by DBV Technologies. K. J. Hildebrand has received a speaker fee from Novartis, is a consultant to Health Link BC Allergy Nutrition services, and was paid travel expenses by AllerGen as allergy expert for management of food allergy in schools systematic review. R. Mak has received honoraria from Novartis, Pediapharm, and Sanofi. T. V. Gerstner has received a grant/research support from Merck and speaker honoraria from Pfizer and Mylan. S. B. Cameron has received an unrestricted educational grant from Pfizer. E. S. Cameron has received research support from DBV Technologies, has been a member of advisory boards for Pfizer, Pediapharm, LEO Pharma, Kaleo, DBV, AllerGenis, Sanofi Genzyme, and Bausch Health, is a member of the Healthcare Advisory Board for Food Allergy Canada, was an expert panel and coordinating committee member of the National Institute of Allergy and Infectious Diseases–sponsored Guidelines for Peanut Allergy Prevention, and is co-lead of the CSACI (Canadian Society of Allergy and Clinical Immunology) oral immunotherapy guidelines. The rest of the authors declare that they have no relevant conflicts of interest.

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Abbreviations used
EoE- Eosinophilic esophagitis
OFC- Oral food challenge
OIT- Oral immunotherapy
P-OIT- Peanut oral immunotherapy
ps-IgE- Peanut-specific IgE
SPT- Skin prick test

(98.3%) tolerated a cumulative dose of greater than or equal to *1000 mg*. For the 25 (21.4%) who reacted, their threshold increased by 3376 mg (95% CI, 2884-3868) from baseline to follow-up; 17 (14.5%) patients experienced grade 1 reactions, 7 (6.00%) grade 2, and 1 (0.85%) grade 3. Two patients (1.71%) received epinephrine associated with P-OIT, and 1 (0.85%) went to the emergency department.
CONCLUSIONS: Our data demonstrate that real-world preschool P-OIT is effective after 1 year of maintenance for those who received a follow-up OFC. For those who reacted, their threshold increased sufficiently to protect against accidental exposures. P-OIT should be considered for preschoolers as an alternative to current recommendations to avoid peanut. **© 2020 American Academy of Allergy, Asthma & Immunology** **(J Allergy Clin Immunol Pract 2021;9:1349-56)**

Key words: *Oral immunotherapy; Preschool; Peanut allergy; Effectiveness; Real-world*

INTRODUCTION

The first study of preschool peanut oral immunotherapy (P-OIT) by Vickery et al[1] demonstrated that P-OIT was effective and safe in 37 preschool-age children; 85% of children on 300 mg daily P-OIT for 29 months were desensitized, there were no severe reactions, and only 1 child required epinephrine.[1] More recent evidence of real-world safety during build-up for 270 preschoolers stems from our group of allergists who initiated "Canadian Preschool Peanut Oral Immunotherapy"; 0.4% experienced a severe reaction, and 4.1% received epinephrine associated with P-OIT dosing.[2]

In older children, a meta-analysis by Chu et al[3] noted a higher rate of anaphylaxis (16.5%) during P-OIT compared with avoidance (2.70%), and concluded avoidance is safer. Efficacy in older children appears to be lower than in preschoolers, according to Grzeskowiak et al,[4] reporting a 68.9% likelihood of a negative exit oral food challenge (OFC) (range, 41.9%-92.3%).

Hypothesized reasons for differences in safety and efficacy in preschoolers include that younger children may have less entrenched food allergy.[5-7] In addition, younger children may not experience subjective symptoms, food aversion, and fear of their food allergens, and may therefore be more adherent and less likely to withdraw from oral immunotherapy (OIT) than older children.[8,9] For these reasons, our study focused on evaluating real-world outcomes of P-OIT in preschoolers.

The primary objective of this study was to evaluate the effectiveness of real-world P-OIT in preschoolers after 1 year of maintenance. Secondary objectives included comparison of baseline characteristics between patients who did and did not receive follow-up OFC, and P-OIT safety during maintenance.

METHODS

Study population

Preschoolers (9-70 months old) were enrolled into the Food Allergen ImmunoTherapy registry from community and academic allergy clinics across Canada. Inclusion criteria were similar to our previous publication in that patients were required to have 1 of the following 2 criteria:

1. History of objective reaction to peanut (at home or during optional baseline OFC to cumulative dose of <300 mg peanut protein), *and* a positive skin prick test (SPT) result (wheal diameter ≥3 mm) or peanut-specific IgE (ps-IgE) level greater than or equal to 0.35kU/L; *or*
2. If no peanut ingestion history and no baseline OFC, a ps-IgE level greater than or equal to 5kU/L was required.[10]

However, to address those patients who did not have a baseline OFC, and to increase the certainty that patients had true IgE-mediated peanut allergy, we generated additional inclusion criteria for the current analysis.

If there was no baseline OFC *and* no peanut ingestion history (or only a grade 1 history[2]), then:
- Both peanut SPT wheal size greater than or equal to 7 mm *and* ps-IgE level greater than or equal to 2 kU/L were required (shown in Australia to correlate with a very high likelihood of true clinical allergy)[11];
- *Plus*: All patients were required to have at least 1 objective reaction with dosing during build-up.

If there was no baseline OFC *and* a grade 2 (or higher) reaction, then:
- Either peanut SPT wheal size greater than or equal to 3 mm *or* ps-IgE level greater than or equal to 0.35 kU/L was required.
- *Plus*: All patients were required to have at least 1 objective reaction with dosing during build-up.

On the basis of these more stringent criteria, a smaller number of patients than the 270 from our previous article[2] qualified for the current analysis.

Contraindications for the current analysis were the same as our previous publication, with 1 exception; this article also included patients who were enrolled with a history of grade 4 reaction.[2]

Procedures

Because this was a real-world study, the decision to perform a baseline OFC (using Bird et al's[12] protocol for infant OFCs[12]) was made on the basis of allergists' available resources (ie, waiting lists) for OFCs.

For build-up, increasing peanut doses were administered in clinic every 2 weeks over 8 to 11 visits to 300 mg peanut protein maintenance, with home daily doses, according to 1 of 3 Canadian Preschool Peanut Oral Immunotherapy protocols published previously (Peanut flour-only, Bamba-only, and Hybrid, which starts with peanut flour at lower doses, and switches to Bamba at the 80-mg dose).[2] These protocols provided flexibility, and no significant differences in safety were identified. Symptoms of allergic reactions were graded 1 to 5,[2] and management of allergic reactions was recorded. Allergists performed baseline SPT and/or measured ps-IgE, and selectively during maintenance and follow-up OFC visits according to clinical discretion. After approximately 12 months' maintenance, patients were invited to an open peanut follow-up OFC.[12]

TABLE I. Comparison of baseline characteristics for patients who did and did not receive the follow-up OFC

Characteristic	All patients	Received follow-up OFC	Did not receive follow-up OFC
Baseline data	N = 161	N = 117	N = 44
Age (mo) at entry into OIT, mean (95% CI)	26.0 (23.9- 28.1)	25.0 (22.5- 27.4)	28.6 (24.5- 32.7)
Sex: male, n (%)	95 (59.0)	70 (59.8)	25 (56.8)
Grade of allergic reaction before entry into OIT, n (%)			
Grade 1	103 (64.0)	79 (67.5)	24 (54.5)
Grade 2	48 (29.8)	31 (26.5)	17 (38.6)
Grade 3	0	0	0
Grade 4	5 (3.10)	4 (3.40)	1 (2.30)
Never exposed, n (%)	5 (3.10)	3 (2.60)	2 (4.60)
Baseline peanut SPT wheal size (mm), mean (95% CI)	7.59 (7.12- 8.06) *based on data from 154 patients*	7.08 (6.62- 7.54)* *based on data from 112 patients*	8.95 (7.83-10.1)* *based on data from 42 patients*
Baseline peanut sIgE level (kU/L), mean (95% CI)	17.7 (12.7- 22.7) *based on data from 115 patients*	12.0 (7.34- 16.7)* *based on data from 80 patients*	30.6 (18.7- 42.6)* *based on data from 35 patients*
Protocol chosen, n (%)			
Bamba-only	24 (14.9)	13 (11.1)	11 (25.0)
Peanut flour-only (capsule)	90 (55.9)	68 (58.1)	22 (55.0)
Hybrid	47 (29.2)	36 (30.8)	11 (25.0)

Note: A total of 13 patients who received the follow-up OFC had an sIgE in the range of those who did not receive the follow-up OFC (ie, sIgE >18.7). Of these, 11 had a negative follow-up OFC and 2 had a positive OFC but had a threshold increase of 3988 and 3955 mg, respectively.
*Statistically significant ($P < .05$) difference between those who did and did not receive the follow-up OFC. All other differences between these 2 groups were not significant.

Study outcomes

The primary effectiveness outcome was the proportion of patients tolerating a cumulative dose of 4000 mg peanut protein without symptoms at follow-up OFC. The secondary effectiveness outcome was the proportion of patients tolerating a cumulative dose of 1000 mg peanut protein at follow-up OFC (this dose is protective against 99% of accidental exposures).[13]

Other outcomes included comparison of characteristics for those who did and did not receive follow-up OFC. For those who had a positive follow-up OFC, grade/treatment of the reaction and cumulative dose eliciting the reaction were calculated. Safety of P-OIT during maintenance was assessed.

We received ethics approval from the Research Ethics Board at University of British Columbia/British Columbia Children's Hospital.

Statistical analysis

Descriptive statistics were compiled for all variables, with the mean and 95% CI being used for all continuous variables where statistical tests were performed. The Mann-Whitney test was used for statistical comparisons between 2 groups, and Kruskal-Wallis test was used for comparisons between 3 or more groups. Per-protocol and "intention-to-treat" analyses were performed to determine the effectiveness of desensitization. Data were analyzed using Stata 15 (StataCorp LLC, College Station, TX).

RESULTS

From April 2017 to February 2018, 185 eligible preschoolers were started on P-OIT, of which 21 (11.4%) dropped out during build-up for various reasons, which were not systematically collected. Of the remaining 164 patients who completed build-up, 3 (1.83%) dropped out on maintenance, leaving 161 patients who were eligble for follow-up OFC. Of the 161 patients, 16 were included in this analysis on a positive baseline OFC alone, 117 with a reaction during build-up alone (these patients did not receive a baseline OFC), and 28 with both a positive baseline OFC and a reaction during build-up.

These 161 patients had a mean age at OIT entry of 26.0 months (95% CI, 23.9-28.1) and most were male (59.0%). Almost all (96.9%) had a history of initial peanut reaction, including 5 (3.10%) with grade 4 reaction; 87.6% of patients in this analysis were managed entirely by allergists in the community, and 92.3% of follow-up OFCs were performed in community allergist offices.

Between February 2018 and December 2019, 117 (72.7%) of the 161 eligible patients received the follow-up OFC after a mean of 12.0 months on maintenance (95% CI, 11.3-12.7), whereas 44 (27.4%) patients did not receive the follow-up OFC (Table I and Figure 1).

Effectiveness of P-OIT

According to the per-protocol analysis, 92 of 117 patients (78.6%) who received the follow-up OFC were able to tolerate cumulative 4000 mg protein without symptoms, and 115 (98.3%) tolerated a cumulative dose of greater than or equal to 1000 mg at follow-up OFC (Figure 2). For those 92 patients with a negative cumulative 4000-mg follow-up OFC, the cumulative dose increased by 3969 mg (95% CI, 3735-4204), from mean 53.6 mg (95% CI, 40.4-66.8) at baseline to mean 4022 mg (95% CI, 3787-4258) at follow-up (Figure 2). SPT wheal size significantly decreased from baseline to follow-up OFC for those with a negative follow-up OFC (mean, 7.03 mm to 3.70 mm) and a positive OFC (mean, 7.24 mm to 5.09 mm) (Figure 3). The Mann-Whitney test identified a significant difference in the magnitude of the decrease in SPT values from baseline to follow-up OFC; SPT wheal size decreased by 43.5% among those with a negative follow-up OFC, whereas it decreased by only 20.2% among those with a positive OFC ($P < .05$). The ps-IgE level also decreased from baseline to follow-up OFC for both groups: mean 11.4 kU/L to 5.66 kU/L in those with a negative OFC and mean 14.1 kU/L to 7.55 kU/L in those with a positive OFC. There was

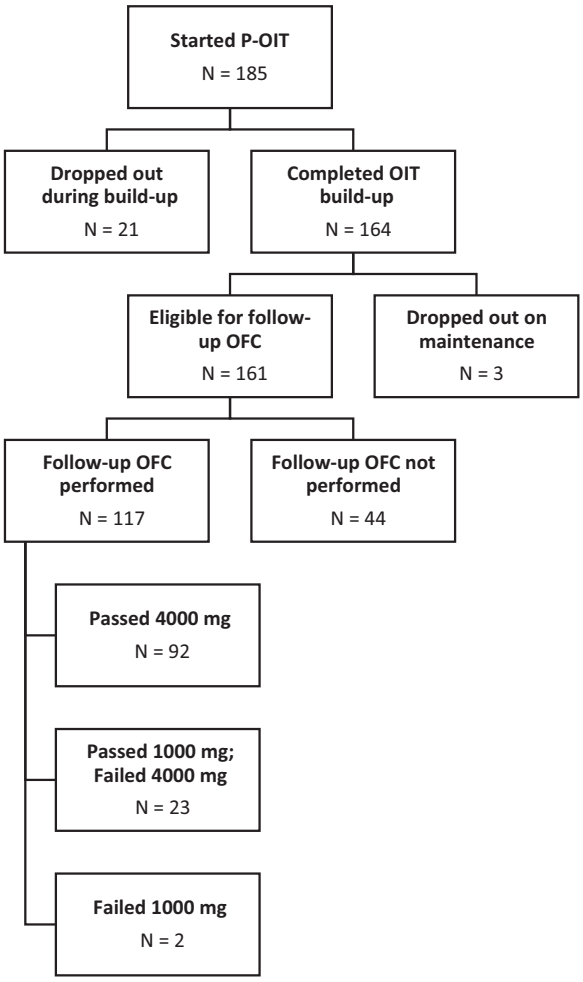

FIGURE 1. Flow diagram of patients enrolled in Canadian Preschool Peanut Oral Immunotherapy who were included in this analysis.

no significant difference in the magnitude of the decrease in ps-IgE values from baseline to follow-up OFC according to the Mann-Whitney test ($P = .25$).

Grade of reaction and cumulative dose for patients with a positive follow-up OFC

Of 25 (21.4%) patients who had a positive follow-up OFC, objective symptoms included 17 (14.5%) grade 1, 7 (6.00%) grade 2, and 1 (0.85%) grade 3 (see Table E1 in this article's Online Repository at www.jaci-inpractice.org). Two (1.71%) patients were treated with epinephrine (1 dose each) and 1 (0.85%) was transferred to the emergency. The cumulative dose increased by mean 3376 mg (95% CI, 2884-3868) from baseline to follow-up OFC for the 25 patients with positive follow-up OFCs, from mean 32 mg (95% CI, 12.2-51.8) at baseline to mean 3408 mg (95% CI, 2933-3883) at follow-up (Figure 2). In addition, 72% of patients who reacted at the follow-up OFC did so only after all doses were consumed. Patients who had a positive follow-up OFC continued daily 300-mg dosing, with a plan to perform a second OFC after 12 to 18 months.

Comparison of baseline characteristics and safety for patients who did and did not receive follow-up OFC

Patients who did not receive the follow-up OFC had higher baseline SPT wheal size (mean, 8.95 mm vs 7.08 mm) and ps-IgE level (mean, 30.6 kU/L vs 12.0 kU/L) than patients who did (Table I). The proportion of grade 2 reactions was greater for those who did not receive the follow-up OFC than for those who did (difference, 19.7%; 95% CI, 3.03%-36.4%), but neither group of patients had grade 3 or grade 4 reactions (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Of those who did not receive the follow-up OFC, 9.1% required epinephrine during build-up, compared with 1.71% for those who did receive the follow-up OFC (difference, 7.39%; 95% CI, −1.43% to 16.2%).

We additionally performed a worst-case scenario imputation ("intention-to-treat" analysis), assuming that all 44 patients who did not receive the follow-up OFC would have reacted, which resulted in 57% effectiveness (92 of 161).

Although the mean baseline ps-IgE level for the 117 who underwent follow-up OFC was 12.0 kU/L, there was a subset of 13 patients with baseline ps-IgE levels greater than 18.7 kU/L (mean, 50.9 kU/L; range, 21.5->100 kU/L) who underwent follow-up OFC. Of these, 11 of 13 (85%) had a negative OFC with mean follow-up ps-IgE level of 28.0 kU/L (range, 2-77 kU/L). For the 2 who had a positive OFC, their increase in threshold was 3988 and 3955 mg protein, respectively.

Safety of P-OIT during maintenance

As of March 4, 2020, 164 eligible preschoolers had started their 300 mg daily maintenance. Of these, 124 (75.6%) returned for in-clinic visits, 28 (17.1%) had not returned for maintenance visits, 9 (5.5%) were excluded because they started OIT to other foods while on P-OIT maintenance, and 3 (1.8%) dropped out. Of the 124 who returned for in-clinic visits and whose safety outcomes were analyzed, 111 (89.5%) did not experience any reactions during maintenance, 10 (8.10%) had grade 1 reactions, and 3 (2.40%) had grade 2 reactions. Two (1.60%) patients received epinephrine associated with P-OIT dosing and 1 (0.80%) patient was transferred to emergency during maintenance.

DISCUSSION

Effectiveness of P-OIT

We are the first to report on the effectiveness of preschool P-OIT in a real-world setting, with 78.6% of those challenged having a negative cumulative 4000-mg OFC after 1 year on OIT maintenance. Evidence suggests that parents desire protection against accidental exposures, different from the primary effectiveness outcome of a negative OFC, which is preferred by most academic publications.[14] According to Baumert et al,[13] an increase in threshold to 1000 mg provides 99% protection from accidental exposures. This patient-centered outcome is best reflected in our secondary outcome, which showed 98.3% tolerating 1000 mg at the follow-up OFC.

In comparing our effectiveness results with results of recent P-OIT studies, key differences in age, dose, and therapy duration likely contributed to differences in outcomes.[1,15,16] Blumchen et al[15] reported 74.2% on P-OIT tolerating greater than or equal to 300 mg at final OFC; only 41.9% of the P-OIT group tolerated 4500 mg protein at the final OFC, much lower than

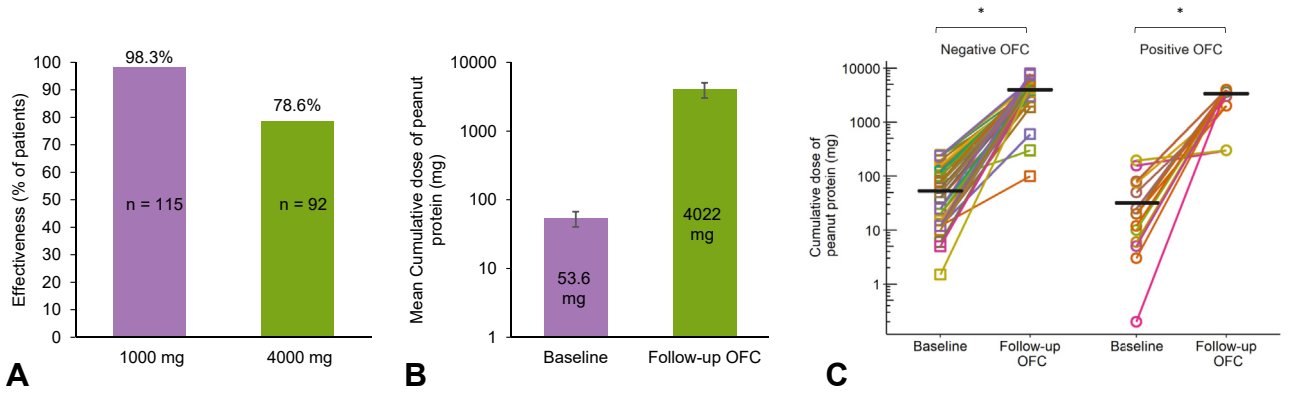

FIGURE 2. Effectiveness of peanut oral immunotherapy. (**A**) Percent of patients (out of 117) tolerating (cumulative) at least 1000 mg protein (98.3%), and 4000 mg (78.6%) at follow-up OFC. (**B**) Mean cumulative dose at baseline (53.6 mg protein) and at follow-up OFC (4022 mg) for the 92 with a negative OFC. Black vertical bars indicate 95% CIs. (**C**) Mean cumulative dose of peanut protein at baseline and follow-up OFC, for the 92 patients who had a negative OFC (squares) and for the 25 patients who had a positive OFC (circles). Each patient is shown in a separate line. Black horizontal lines represent mean values (on logarithmic scale). The difference in the mean value between baseline and follow-up OFC was calculated and was considered statistically significant if the 95% CI for the difference did not cross 0, denoted by * in the figure above.

our 78.6%. Key differences in methodology are that Blumchen et al had a higher median age, shorter duration of maintenance, lower maintenance dose, and many more in-office build-up visits (33 vs our 8-11 visits). PALISADE (Peanut Allergy Oral Immunotherapy Study of AR101 for Desensitization in Children and Adults) reported 67.2% on 300 mg peanut protein maintenance ingesting 600 mg eliciting dose (cumulative, 1043 mg) protein without symptoms at exit OFC.[16] This result is substantially lower than ours, where 98.3% of patients challenged after 1 year of maintenance tolerated greater than or equal to 1000 mg. PALISADE participants were much older (and therefore had more significant symptoms by history) and the duration of maintenance was shorter. Vickery et al[1] reported 85% desensitization in preschoolers to 5000-mg OFC in the intention-to-treat analysis. Despite our maintenance duration before OFC being shorter (1 year vs 2.5 years) than Vickery et al, our effectiveness was comparable, providing further insight into how much more "pliable" the immune systems in preschoolers are compared with older children.

Comparison of baseline characteristics and safety of patients who did and did not receive follow-up OFC

Although patients who did not receive the follow-up OFC had significantly higher baseline SPT wheal size and ps-IgE level than those who did, they were similar to those who received the follow-up OFC in all other domains. This is a real-world study, with 87.6% of patients treated in community allergist offices. Therefore, there are additional practical factors that could influence whether to offer the follow-up OFC, which were not evaluated in this study, including lack of resources or family hesitancy.

To satisfy any remaining concerns about the 44 not receiving the follow-up OFC, our worst-case scenario analysis, although highly unlikely, still yielded an impressive effectiveness of 57% who would have had a negative cumulative 4000-mg follow-up OFC. This would still be higher than PALISADE, with 67% of patients tolerating a cumulative dose of approximately 1043 mg protein at the exit OFC.[16] We were also reassured that a subset of the 117 had higher ps-IgE level in the range of the levels for the 44, with 85% having a negative follow-up OFC despite follow-up ps-IgE level of 28.0 kU/L.

Safety of P-OIT during maintenance

Our data demonstrated that only 9.5% experienced allergic reactions (8.10% grade 1, and 2.40% grade 2) and 1.60% received epinephrine during maintenance. Similarly, Vickery et al[1] did not identify any preschoolers who required epinephrine during maintenance. In stark contrast, Wasserman et al[17] in 2014 reviewed real-world OIT across 5 centers and found 6% of patients aged 3 to 24 years on maintenance required epinephrine; in 2018, they[18] reported 63 epinephrine-treated reactions in 28 patients on maintenance (40% during the first 6 months on maintenance, and 57% in the first year). Our previous study of safety during build-up reported a 0.37% biopsy-proven rate for eosinophilic esophagitis (EoE),[2] with no additional patients developing EoE during maintenance in the current study; this rate is lower than the 2.7% who developed EoE as described by Lucendo et al.[19] We hypothesize that in preschoolers the risk of developing EoE while on OIT is lower than in older children, although this warrants more research. Overall, safety during maintenance appears to be much better in preschoolers than in older children.

A common argument against offering OIT is that the risk of anaphylaxis is higher than with avoidance. A recent meta-analysis reported 16.5% anaphylaxis on P-OIT with 11.8% requiring epinephrine, whereas 2.7% on "no OIT" (largely placebo groups in clinical trials) had anaphylaxis and 3.7% of these required epinephrine.[3] This meta-analysis of older children (median, 8.7 years) estimated that P-OIT was associated with 151 more episodes of anaphylaxis per 1000 patients than placebo/avoidance.[3] However, the authors did not take into account that reactions during OIT typically occur as intentional/anticipated exposures, whereas those practicing avoidance experience unpredictable/unanticipated reactions, which can be more stressful.[20] Recently,

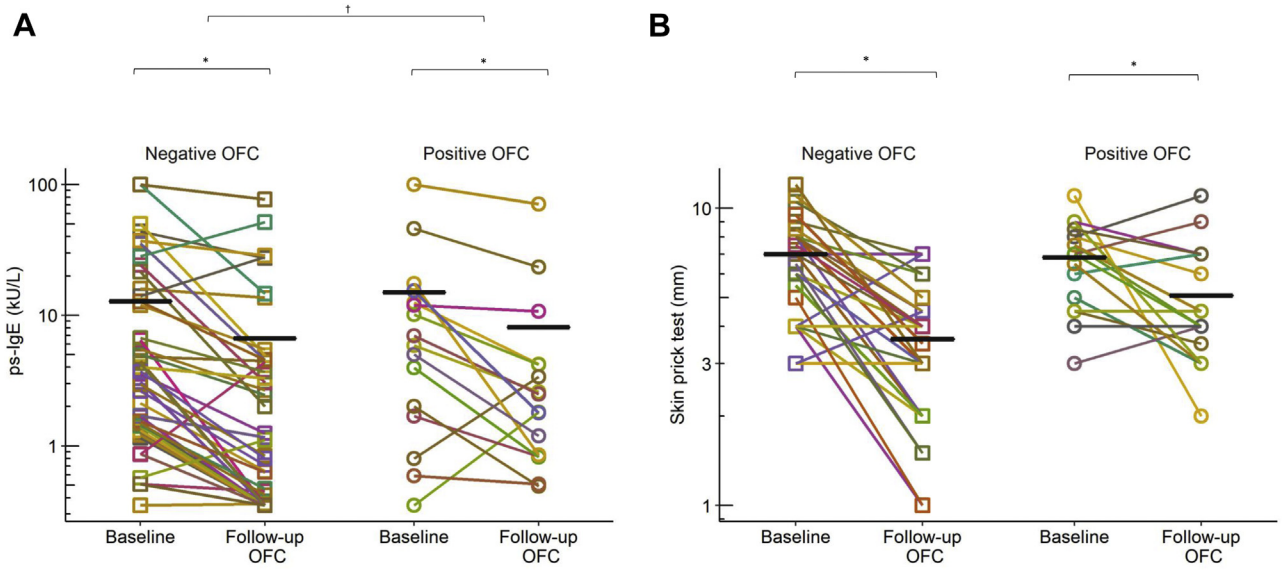

FIGURE 3. Immunologic changes from baseline to follow-up OFC. Shown are wheal size diameter of (**A**) peanut SPT and (**B**) ps-IgE level. Black horizontal lines represent mean values (on logarithmic scale). Squares represent patients who had a negative OFC; circles represent patients who had a positive OFC. Each patient is shown in a separate line. For the comparison of baseline and follow-up OFC data within a group, the difference in the mean (SPT or IgE) value between baseline and follow-up OFC was calculated, and was considered statistically significant if the 95% CI for the difference did not cross 0, denoted by * in the figure above. For the comparison across groups, the Mann-Whitney test was used to compare the decrease (in SPT or IgE value) from baseline to follow-up OFC for those who had a negative vs those who had a positive follow-up OFC, and significance was defined as *P* less than .05, denoted by † in the figure above.

Kansen et al[21] followed children in the real world after positive double-blind placebo-controlled food challenge, showing that avoidance may not be as safe as Chu et al[3] concluded, with 41% experiencing accidental allergic reactions and 29% experiencing severe symptoms (with many having severe lower respiratory tract symptoms) over a 3-year period, suggesting 9.8% annual risk of anaphylaxis. Of most concern, none of the children experiencing severe symptoms received epinephrine, despite clear instructions for how/when to use epinephrine. HealthNuts as well as a review by Capucilli et al recently showed a similar rate of anaphylaxis (and extreme underutilization of epinephrine) with avoidance as Kansen et al.[21-23] The difference in annual rate of anaphylaxis between Chu et al and Kansen et al, HealthNuts, and Capucilli et al (2.7% vs ~10%) could be due to Chu et al analyzing data mainly on clinical trial subjects who are closely followed and more adherent, whereas the more recent studies collected data from real-world patients. Another hypothesized reason for the difference is the time period under study; it is expected that reactions during build-up and early maintenance for OIT (the time period analyzed by Chu et al) are increased, but presumably, over the long-term, these patients will have fewer reactions than controls who will continue to have similar annual risk.

A criticism of performing P-OIT outside of research is that, over time, nonadherence would increase, which is problematic because maintaining desensitization requires regular ingestion.[24] Dantzer et al[25] reported that after a median of 7.8 years participating in P-OIT clinical trials, only 11 of 21 (52%) patients were consuming peanut regularly, an outcome that was interpreted negatively by the authors. Importantly, all 4 patients who had a negative exit OFC were consuming peanut regularly, and it was unsurprising that many of the other 17 patients (who had all failed escalation, maintenance, or had a positive exit OFC) would not be eating peanut regularly.[25] A recent follow-up survey of past participants in OIT and sublingual immunotherapy trials reported that 89% of subjects continued peanut consumption after median 2.9 years, with 64% consuming peanut daily.[26] Interestingly, median age at entry into these trials was 3.5 years, which could partly explain higher adherence to peanut consumption than the Dantzer et al[25] study. To mitigate long-term nonadherence, Nachshon et al[27] suggested reducing the OIT dose, reporting that 3.9% of patients consuming 1200 mg daily dropped out compared with 27.8% consuming 3000 mg daily. Wasserman et al[18] found that 11.7% discontinued on 3000 mg maintenance.[18] On the basis of our low dropout rate during maintenance (1.83%), we hypothesize that our lower maintenance dose, combined with preschool age, less aversion/anxiety in the preschooler, and greater parental supervision, may help improve adherence. We hypothesize that once preschoolers have eaten peanut regularly post-OIT for roughly a decade before reaching the less-adherent adolescent years, tolerance will probably occur.

Study Limitations

As a real-world study, our data have significant strengths that contribute to the application, practical evaluation, and external validity of this treatment for both allergists and families, and have potential to improve shared decision making about benefits/limitations of P-OIT based on the pragmatic nature of the study design. However, there are inherent methodologic limitations of real-world studies, including that baseline OFCs were not mandatory. Our group of predominantly community allergists, managing almost 90% of the patients in this analysis, were

willing to do baseline OFCs when clinically indicated; however, most patients (74.4%) did not receive them for practical reasons (resource limitations) as well as poor patient acceptability of OFCs when pretest probability was high, which has inherent risks and has in the past led to a reported fatality.[28] However, we do feel that practitioners not willing or able to perform OFCs should not offer OIT, because OFCs may still be required at baseline for diagnosis and are absolutely required at follow-up to assess desensitization and/or tolerance.

The lack of mandatory baseline OFCs was an intended feature of this study, to increase relevance to allergists who do not have the resources to conduct baseline OFC on all patients. The goal of pragmatic research is to identify whether an intervention works under usual circumstances, as seen in community allergist clinics, instead of ideal circumstances, as seen in randomized controlled trials. Pragmatic study designs maximize external validity and increase "real-world" applicability. To mitigate the risk that our patients did not have true peanut allergy, and given historical data that 20% outgrow peanut allergy before age 5 years,[29] we included only those patients who fit stringent inclusion criteria. The combination of SPT wheal size greater than or equal to 7 mm and ps-IgE level greater than or equal to 2 kU/L in those with unknown previous clinical reactivity was shown by Australian investigators to correlate with 89% likelihood of true peanut allergy, suggesting that our cohort had at least that degree of certainty if not higher.11 Patients who met these testing criteria also reported OIT-related symptoms during dosing, thus clinically confirming they were peanut-allergic.

Criticisms that our patients have "milder" peanut allergy could possibly be because the vast majority of preschoolers inherently often have a milder phenotype of peanut allergy, with less severe reactions and lower test results than older children.[1,6] Regardless, the benefit of treating peanut allergy early rather than waiting until the child is older and develops a more entrenched "severe" peanut allergy phenotype cannot be underestimated.

Because follow-up OFC was not mandatory, allergists selecting certain patients with favorable biomarkers (low SPT wheal size/ps-IgE level for example) could potentially have led to an overestimate of effectiveness. However, given this was a real-world study, these results reflect what other similar practices might experience when attempting P-OIT in their patients. Also, we have accounted for this potential bias in our intention-to-treat analysis, which still demonstrates very effective outcomes.

CONCLUSIONS

We found that 78.6% of preschoolers who received P-OIT had a negative cumulative 4000-mg protein OFC after a mean of 1-year maintenance. What may be a more meaningful outcome for many parents is the protection from accidental exposures (to 1000 mg protein) P-OIT provided for 98.3% of preschoolers. The rate of epinephrine administered during maintenance (1.60%) was low, and we expect these reactions will become even less frequent over time. Even with a worst-case scenario imputation adjusting for those who did not receive the follow-up OFC, our effectiveness would still be high and our threshold increase would provide more than adequate protection from accidental exposures. We will continue to follow this cohort long-term, which we expect will further strengthen our recommendations.

Real-world P-OIT is effective in preschoolers who received follow-up OFC after a mean of 1-year maintenance. With long-term study data, OIT could be more routinely offered to preschoolers to prevent potential long-term consequences of food allergy, including anxiety, poor quality of life, social isolation, higher reaction risks with avoidance in the real-world than previously appreciated, and lower safety/effectiveness if OIT is attempted at an older age.

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TABLE E1. Grade of reaction and cumulative dose for patients with a positive follow-up OFC

Cumulative dose	Grade 1	Grade 2	Grade 3	Total
300	1	1	0	2
2000	3	0	0	3
3000	0	1	0	1
3600	1	0	0	1
4000	12	5*	1†	18
Total	17	7	1	25

Note: There were no grade 4 or grade 5 reactions during the follow-up OFC.
*One patient received epinephrine.
†One patient received epinephrine and went to the emergency department.

TABLE E2. Comparison of safety outcomes for patients who did and did not receive the follow-up OFC

Outcome	All patients	Received follow-up OFC	Did not receive follow-up OFC
Baseline data	N = 161	N = 117	N = 44
Highest grade of reaction during baseline OFC or build-up, n (%)			
Grade 1	78 (48.4)	63 (53.8)	15 (34.1)
Grade 2	83 (51.6)	54 (46.2)*	29 (65.9)*
Grade 3	0	0	0
Grade 4	0	0	0
Received epinephrine, n (%)	6 (3.70)	2 (1.71)	4 (9.1)

*Statistically significant difference between those who did and did not receive the follow-up OFC. All other differences between these 2 groups were not significant.