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Dosing Reactions and Missed Doses Affect Peanut Oral Immunotherapy Outcomes

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Abstract

Background: Peanut oral immunotherapy (pOIT) is a recognized treatment for patients with peanut allergy, though not all patients who undergo this therapy achieve desensitization or remission.

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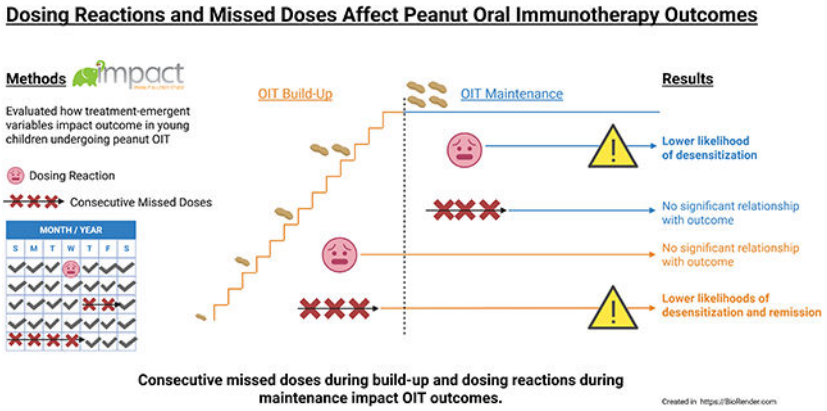
Objective: To determine whether missed doses or dosing-reactions predict clinical outcomes with pOIT.

Methods: Data from the IMPACT trial, a randomized, double-blind, placebo-controlled trial of pOIT in children aged 1 to 4 years with peanut allergy, was analyzed to determine whether treatment-emergent variables influence desensitization (ability to consume 5000mg of peanut protein without reaction during a blinded oral food challenge after 134 weeks of pOIT) and remission (six months after discontinuation of pOIT). Logistic regression models, controlling for age and Ara h2-specific IgE, were performed to assess the relationship between dosing reactions, missed doses, and outcomes.

Results: Consecutive missed doses during build-up significantly correlated with reduced likelihood of desensitization (p = 0.03, OR 0.69 (0.49, 0.96)), whereas consecutive missed doses during maintenance did not (p = 0.10, OR 0.79 (0.59, 1.05)). Furthermore, the total individual missed doses did not significantly correlate with desensitization or remission in either phase of pOIT. Conversely, dosing-reactions during maintenance did significantly correlate with reduced likelihood of desensitization (p = 0.01, OR 0.71 (0.54, 0.93)) while dosing-reactions during build-up did not significantly correlate with desensitization (p = 0.57, OR 0.95 (0.79, 1.14)). Fewer than 10% of missed doses were attributed to dosing reactions.

Conclusions: Missed doses during therapy and dosing-reactions during maintenance associated with poorer pOIT outcomes. Clinicians should support adherence during build-up and consider dose adjustments for patients having dosing-reactions during maintenance therapy.

Graphical Abstract



Keywords

Food allergy; Oral immunotherapy; Peanut allergy; Efficacy; Safety

Introduction

Peanut allergy is a common and often severe food allergy in children. The prevalence of peanut allergy has been increasing in recent decades, with studies showing that it affects approximately 2% of children in Western countries, although rates can vary by region and ethnicity. (1–4) Peanut allergy is lifelong for the majority of affected individuals.

(5,6) Despite advancements in our understanding of peanut allergy, there is no cure for peanut allergy, and the focus remains on prevention, early diagnosis, and treatment to reduce the risk of allergic reactions.(7–10) In recent years, treatments for peanut allergy have moved away from strict avoidance to include therapeutic interventions such as peanut oral immunotherapy (pOIT), which provides desensitization to peanut and an increased protection in case of accidental ingestion. (11–14) Furthermore, a subset of children who undergo pOIT achieve remission, a state of non-responsiveness after discontinuation of immunotherapy. (11,13,15,16) Peanut OIT is also associated with an improvement in quality of life in peanut allergic patients and their caregivers. (17,18)

Oral immunotherapy is not without risks. (16,19–22) Given the inherent risks and burden of pOIT, it is crucial to identify which patients are most likely to benefit from pOIT and who will achieve desensitization or remission after pOIT. Multiple studies have shown that younger age, a higher baseline peanut-specific IgG4 to peanut-specific IgE ratio, and lower baseline Ara h2-specific IgE and peanut-specific IgE are associated with positive clinical outcomes following pOIT. (12,16,20,23,24) The most commonly described clinical predictor of successful pOIT is younger age. (13,23) However, Lloyd et al. also found that a low reaction-eliciting dose at the initiation of pOIT, and comorbid allergic diseases, such as multiple food allergies and self-reported history of wheeze and asthma, reduced the likelihood of achieving remission after pOIT. (15) Although factors such as older baseline age, higher baseline peanut-specific IgE, comorbid allergic rhinitis, and pre-OIT initial grade 2+ reactions are associated with an increased risk of adverse reactions during pOIT, data describing the impact of treatment-emergent variables such as dosing-compliance and dosing-reactions on the outcome of pOIT are lacking. (21,23)

To date, there are no validated biomarkers that predict which patients will achieve desensitization or remission. In the Oral Immunotherapy for Induction of Tolerance in Peanut Allergic Children trial (IMPACT, ITN050AD, NCT01867671), pOIT administered to children ages 12 months to 48 months was safe and efficacious. A younger age at screening and lower baseline peanut-specific IgE predicted remission, suggesting a therapeutic window of opportunity for early intervention. (13) Here, we assessed the association of treatment-emergent variables, including missed doses and adverse dosing-reactions on the outcomes of desensitization and remission in the IMPACT participants.

Methods

Study Population, Design, and Procedures

The IMPACT trial was a randomized, double-blind, placebo-controlled, multicenter study that compared pOIT to placebo in peanut-allergic pre-school-aged children.(13) The study enrolled participants between August 13, 2013, and October 1, 2015. Eligible participants aged 12 to <48 months with a history of peanut allergy or avoidance, elevated peanut-specific IgE (≥5 kUA/L), a positive peanut skin-prick test (SPT) (wheal >3mm to peanut compared to placebo) and proven clinical reactivity to <500 mg peanut protein at the time of study entry were randomized to receive either pOIT at a target maintenance dose of 2000mg of peanut protein or a placebo (oat flour) for 134 weeks. Double-blind, placebo-controlled food challenges (DBPCFC) to 5000mg of peanut protein were conducted at baseline and at

the end of the dosing phase (week 134). Participants who tolerated the 5000mg of peanut protein at the week 134 challenge were categorized as desensitized. All participants then discontinued pOIT and avoided peanut for 26 weeks. Regardless of their week 134 DBPCFC outcome, a follow-up DBPCFC at week 160 to 5000mg of peanut protein was conducted. Participants who tolerated the week 160 challenge were considered to have achieved remission. The intention-to-treat (ITT) population (all randomized participants) were the focus of the initial efficacy report (13). Here we focus on the per protocol population; participants with an oral food challenge at week 134 or week 160. Written informed consent was obtained from guardians of the participants. Institutional Review Boards at each of the five academic medical centers approved the study protocol. The study was conducted under a Food and Drug Administration investigational new drug application and monitored by a National Institutes of Health - National Institute of Allergy and Infectious Diseases Data and Safety Monitoring Board. The trial is registered on ClinicalTrials.gov, NCT03345160 and the protocol has been previously published. (13)

Definition of Build Up and Maintenance Dosing Phases

Participants underwent an initial dose escalation at the start of the study, which was a single day during which participants received multiple doses of peanut flour or placebo with incremental increases every 15–30 minutes until a dose of 6 mg peanut protein or placebo was consumed. A minimum tolerated dose of 1.5 mg peanut protein (3mg of peanut flour) or placebo flour was required to remain in the study. Participants then returned the following morning for an observed single-dose administration of their highest tolerated dose from the preceding day. Daily dosing of pOIT was then continued at home with an observed dose escalation every 2 weeks during the build-up phase until the target maintenance dose of 2000mg of peanut protein was reached. The expected build-up phase was 30 weeks. Participants who did not reach the target dose could still enter the maintenance phase at their highest tolerated dose, defined as a minimum of 250mg of peanut protein or placebo flour. Participants then continued on daily maintenance pOIT for 104 weeks (total 134 weeks) prior to avoidance (through week 160).

Assessment of Dosing Compliance and Dosing Reactions

Home dose-related symptoms and adherence were tracked through daily study diaries, via contact with the study team, and drug accountability logs that were reported in the electronic data capture system. Oral immunotherapy dosing-induced reactions were defined as related to dosing if they occurred within 2 hours of dose administration. Dosing reactions were scored as mild, moderate, or severe using an adapted grading system from the Consortium of Food Allergy Research (CoFAR3) (See Table EI in the online repository). (25)

Skin Prick Test and Immunoglobulin Measurements

Serum biomarkers and SPTs were collected at baseline and at weeks 30, 82, 134, and 160 of the study. SPT was performed with peanut extract, saline, and histamine (Greer Laboratories, Lenoir, NC, USA). Serum immunoglobulins were measured by ImmunoCAP 1000 system (Viracor Eurofins, Lee’s Summit, MO), and plasma IgE and IgG4 to peanut components (Ara h1, 2, 3, 6) were measured using the ImmunoCAP 250 system (Phadia-Thermo Fisher Scientific, Waltham, MA) as previously described. (13)

Statistical analysis

All assessments for this analysis were performed on the per protocol population. The sample size consisted of all participants in the per protocol population with non-missing values of all variables considered in the analysis. Imputation of desensitization and remission were not done.

Demographics and baseline characteristics were assessed by participant's combined DBPCFC status at week 134 and week 160. Participants who did not tolerate the 5000mg dose at week 134 challenge were categorized as not desensitized. Participants who tolerated the 5000mg dose at the week 134 challenge and did not tolerate the 5000mg dose at the week 160 challenge were categorized as desensitized, and participants who tolerated the 5000mg dose at the week 160 challenge were categorized as achieving remission. Median and interquartile range were calculated for continuous variables within each overall DBPCFC status, and groups were compared using the Kruskal-Wallis test. Frequencies and percentages were calculated for categorical variables within each overall DBPCFC status, and groups were compared using the χ^2 test (or Fisher's exact test when necessary).

Treatment-emergent variables during pOIT, including the number of missed daily pOIT doses, the maximum number of consecutive missed doses (considering all occurrences of consecutive missed daily pOIT doses), the number of dosing reactions (the number of days with at least one dosing reaction to daily pOIT), and the severity of dosing reactions (considering the maximum graded severity each day a dosing reaction occurred) were calculated within each study phase (build-up, maintenance, and combined build-up and maintenance).

Multivariable logistic regression analyses were used to assess the effect of each pOIT dose-related metric on desensitization and remission. All regression analyses included one pOIT dose-related metric and adjusted for the baseline age of the participant (in months) and baseline Ara h2-specific IgE. Adjusted odds ratios (and associated 95% confidence intervals) of tolerating the 5000mg dose at the DBPCFC for desensitization at week 134 and remission at week 160 were calculated for each dose-related metric. A p-value was obtained to quantify the statistical significance of the relationship between each pOIT dose-related metric and each outcome (desensitization or remission). Lastly, to determine if there was an interaction between age, baseline Ara h2 IgE, and the maximum cumulative missed doses, a Pearson correlation coefficient was calculated. All analyses are exploratory, and no adjustments for multiple comparisons were performed.

Results

Participant Overview

Of the 209 participants enrolled in the trial, 146 were randomly assigned to pOIT (96 participants) or placebo (50 participants). 81 of those randomized to pOIT met per protocol criteria and completed the week 134 DBPCFC to peanut. A total of 70 participants randomized to pOIT completed the avoidance period and the week 160 DBPCFC to peanut (see Figure E1 in the online repository). The baseline demographics and dosing metrics of the per protocol group are summarized in Tables I and II. The baseline characteristics,

including comorbidities, peanut allergy history, and peanut wheal size, were similar between the participants when grouped by outcomes (not desensitized, desensitized, and remission), with the exception of age at time of screening, and the cumulative tolerated dose (CTD) of peanut at the screening DBPCFC. In particular, younger age and higher baseline CTD were features of the group achieving remission. Lastly, the maximum maintenance dose and average daily maintenance dose were significantly different between the outcome groups with higher maintenance doses noted among those achieving remission compared to those not reaching remission, although the dose ranges overlapped (Table II).

Biomarkers

Baseline serum biomarker comparisons among participants receiving pOIT revealed distinct differences between the treatment outcome groups (Table I). Participants who achieved remission had significantly lower baseline Ara h2-specific IgE, peanut-specific IgE, and peanut-specific IgE/total IgE ratio, and a significantly higher baseline peanut-specific IgG4/IgE ratio compared to participants who did not achieve remission.

Baseline biomarkers were assessed for association with desensitization and remission using a simple logistic regression analysis. Of the biomarkers, baseline age (in months) ($p= 0.002$) and Ara h2-specific IgE ($p = 0.004$) negatively associated with remission significantly. After adjusting for age, a higher baseline peanut-specific IgE ($p = 0.02$) negatively associated with desensitization but not remission, while both the baseline peanut-specific IgE/total IgE and baseline peanut-specific IgG4/IgE ratios negatively associated with remission ($p = 0.004$ and $p = 0.01$ respectively) but not desensitization ($p = 0.057$ and $p = 0.15$ respectively). Baseline Ara h2-specific IgE negatively associated with both desensitization ($p = 0.03$) and remission ($p = 0.02$) significantly. Neither baseline peanut-specific IgG4 nor baseline peanut-specific IgG4 Ara h2 associated with remission after adjusting for age. Furthermore, biomarker change from baseline over the course of the trial did not associate with clinical outcomes for any of the biomarkers. Based on these results, baseline age and baseline Ara h2-specific IgE were included in all subsequent models.

Missed Doses

There was no significant association between the total number of missed doses and either outcomes of desensitization or remission during any phase of pOIT (Figure 1a–c). The median (IQR) number of missed doses for those who tolerated the desensitization challenge was 30.0 (IQR 11.8–50.0) and for those who did not tolerate the desensitization challenge was 34.0 (IQR 27.0–94.0). The median number of missed doses for those who tolerated the remission challenge was 27.5 (IQR 10.0–36.0), and 34.5 (IQR 15.3–64.3) for those who did not tolerate the remission challenge.

However, the maximum number of consecutive missed doses during build-up negatively associated with desensitization ($p = 0.03$, OR 0.69 (0.49, 0.96)), whereas the maximum consecutive missed doses during the maintenance phase did not significantly associate with desensitization ($p = 0.10$, OR 0.79 (0.59, 1.05)) (Figure 2a–b). Combining the build-up and maintenance phases of the study, the maximum number of consecutive missed doses significantly and negatively associated with both desensitization ($p= 0.01$, OR 0.68 (0.50,

0.92)) and remission (p = 0.02, OR 0.62 (0.41, 0.94)). (Figure 2c). The maximum number of consecutive doses missed ranged from 0–8. The median (IQR) consecutive missed doses for participants who achieved desensitization was 2.0 (IQR 2.0–4.0) compared to 5.0 (IQR 2.0–6.0) in non-desensitized participants; and 2.0 (IQR 0–3.0) for participants who achieved remission and 3.0 (IQR 2.0–4.0) for those that did not. Additionally, of the 81 participants who were included in the desensitization analyses (at Week 134), 50 had more than one occasion of two or more consecutive missed doses. Of the 70 participants who were included in the remission analyses (at Week 160), 42 had more than one occasion of two or more consecutive missed doses. In either analysis population, multiple occasions of consecutive missed did not have a significant impact on the desensitization and remission outcomes. However, maximum number of consecutive missed doses did impact outcome.

After excluding 3 participants who did not reach a maintenance dose of 1600mg of peanut protein, sensitivity analysis showed a negative association between the maximum number of consecutive missed doses during build-up and desensitization, though the results did not reach significance (p = 0.07, OR 0.75 (0.55, 1.02)). However, for the combined build-up and maintenance phases of the study, the association between maximum number of consecutive missed doses and desensitization ((p = 0.03, OR 0.68 (0.49, 0.96)) and remission remained significant (p = 0.02, OR 0.62 (0.41, 0.94)) (See Figure E2 in the online repository).

Reasons for consecutive missed doses

The most common reasons for missed doses were concurrent illness and participant/guardian forgetting to administer the dose (Table III). Approximately, only 6.5% of consecutive missed doses were attributed to therapy-related reactions during home dosing. The reasons for missed doses during pOIT are shown grouped by outcomes in Table EII in the Online Repository.

Dosing Reactions

The total number of dosing reactions during build-up did not significantly associate with desensitization (p = 0.57, OR 0.95 (0.79, 1.14)) nor remission (p = 0.50, OR 0.89 (0.63, 1.26)) (Figure 3a). However, the total number of dosing reactions experienced during the maintenance phase was significantly and negatively associated with desensitization (p = 0.01, OR 0.71 (0.54, 0.93))(Figure 3b) but not remission (p = 0.52, OR 0.90 (0.65, 1.25)) (Figure 3c). Categorizing the adverse reactions by CoFAR3 grading system for allergic reaction (See Table EI in the online repository), mild reactions (median 17.0, IQR 7.0–32.0) occurred more frequently than moderate reactions (median 0.00, IQR 0.0–2.0). Furthermore, the number of both mild and moderate dosing-related reactions were higher in the build-up phase compared to maintenance. Four severe dosing-related reactions occurred with at-home pOIT dosing in two participants during build-up, and two participants during maintenance. Three of these 4 participants achieved desensitization and none achieved remission.

Mild dosing reactions during build-up did not significantly associate with clinical outcomes (Figure 4a) but mild dosing reactions during maintenance negatively and significantly associated with desensitization (p = 0.03, OR 0.73 (0.54, 0.97) (Figure 4b). Moderate reactions during build-up (p = 0.02, OR 0.00 (0.00, 0.23)) and maintenance (p = 0.01, OR

0.01 (0.00, 0.36)) phase both separately, and when both phases are combined together (p = 0.005, OR 0.02 (0.00, 0.29)), negatively associated with desensitization only (Figure 4a–c).

After exclusion of 3 participants who did not reach a maintenance dose of 1600mg of peanut protein, sensitivity analysis showed a negative association between the total number of dosing reactions during maintenance and desensitization. This association remained significant and largely unchanged (p = 0.01, OR 0.69 (0.52, 0.91)) when compared to the primary analysis. Sensitivity analysis of mild dosing reactions was also similar to the primary analysis. Mild dosing reactions during maintenance negatively associated with desensitization (p = 0.02, OR 0.70 (0.52, 0.95) and reached significance. However, unlike the primary analysis, moderate reactions negatively associated with desensitization only during the maintenance and combined build-up/maintenance phases. Significance was no longer observed at the desensitization endpoint during build-up.

A graphical representation, using a 3-dimensional bubble plot, captures the distribution of participants' baseline age, baseline Ara h2 IgE, and the maximum cumulative missed doses, grouped by desensitization and remission (Figure 5). Participants who achieved desensitization and remission are clustered around lower baseline age, baseline Ara h2 IgE, and cumulative missed doses. To determine if there was an interaction between age, baseline Ara h2 IgE, and the maximum cumulative missed doses, a Pearson correlation coefficient was calculated. There was a weak positive correlation between baseline age and cumulative missed doses (r = 0.14, p = 0.187) and a weak negative correlation between baseline Ara h2 IgE and cumulative missed doses (r = −0.02, p = 0.853) that did not reach significance.

Discussion

Here, we describe for the first time the potential impact of missed doses and dosing-reactions on clinical outcomes in peanut oral immunotherapy. Controlling for baseline age and baseline Ara h2-specific IgE, we found that the maximum number of consecutive missed doses during the build-up phase and the number of dosing reactions experienced during the maintenance phase were both associated with a lower likelihood of achieving positive clinical outcomes, desensitization and remission. These data suggest that the extent of consecutive missed does and dosing reactions not only predict clinical outcomes but that their timing during the treatment phases of pOIT may also matter, acknowledging that the OR estimates are similar between the treatment phases. Adherence to the daily dosing regimen could be especially important during the build-up phase of the pOIT protocol. Interestingly, the most common reason for missed consecutives doses was concurrent illness, followed by parent/guardian forgetting to administer the dose.

These findings have practical real-world implications for pOIT protocols, clinicians, patients, and their families (See Table EIII in the Online Repository). For example, in addition to education for parents and caregivers on the importance of adherence to OIT protocols, build-up phases could be timed to support compliance by avoiding cold and flu season and busy sports schedules, thus minimizing the likelihood of consecutive missed doses. The effect of interruptions in dosing sequence on other clinical outcomes in food OIT protocols has also been investigated, and one study of milk OIT showed that adherent

patients had lower incidence of allergic reactions, anaphylaxis, health care/ER visits, and epinephrine/antihistamine use compared to non-adherent patients. (26)

There was no significant correlation between the maximum total number of missed doses during the maintenance phase and clinical outcome, suggesting that missing 1 or 2 doses, even repeatedly, during maintenance may not significantly affect clinical outcomes. Daily dosing carries a significant burden to patients and caregivers and other studies have shown that some parents/guardians of infants and toddlers with peanut allergy elect not to pursue pOIT because of the need for daily dosing. (27,28) An open-label extension study of pOIT in older children and adolescents found that daily dosing led to higher rates of desensitization than non-daily dosing.(29) There may possibly be differences in the need for daily dosing during maintenance depending on the age at which pOIT is initiated. Future studies are needed to confirm if less frequent dosing during the maintenance phase yields similar desensitization and remission outcomes as does daily dosing in the infant/toddler age group.

While dosing reactions were not a common reason for missed doses, dosing reactions that occurred during the maintenance phase negatively affected desensitization. Dosing reactions are common with pOIT and the majority of participants do experience some dosing-induced symptoms, particularly during the build-up phase. (30) The higher rate of dosing reactions experienced during buildup is likely due to the administration of escalating doses of peanut protein and potential for allergic reaction with each dose increase. In contrast, the risk of dosing reactions during maintenance is likely lower due to the stable dose exposure and the development of desensitization. While previous evidence on the effects of dosing-reactions on desensitization or remission is lacking, factors that influence the likelihood of dosing-reactions and reaction severity during pOIT have been studied. Factors such as infection, exercise, nonadherence, menstruation, temperature changes, and uncontrolled asthma may increase the risk of dosing-reactions. (30,31) The timing of daily dose ingestion may also be relevant, as evening ingestion has been described as a potential variable that increases the risk of reactions requiring epinephrine during pOIT in children. (32) Additionally, Virkund et al. found that allergic rhinitis is a significant predictor of adverse events during pOIT and patients with allergic rhinitis were more likely to experience these adverse events during peak pollen months.(33) The findings from this study supports continued clinician and patient/parent shared decision-making in when to start pOIT and during treatment if the patient is having continued reactions during the maintenance phase. Treatment modifications, and perhaps discontinuation, should be considered for significant dosing reactions during the maintenance phase of pOIT.

A strength of this study is that the data come from a well-characterized participant population, allowing for control of biomarkers associated with pOIT outcomes, as well as carefully recorded data on daily dosing adherence and reactions. Additionally, the outcomes were assessed with DBPCFCs. Similar to the previously reported studies that showed age, baseline peanut-specific IgE, baseline Ara h2-specific IgE were associated with positive clinical outcomes after pOIT(12,15,19,22), here, both age and baseline Ara h2-specific IgE were each significantly associated with remission and when combined into a single model, were both significantly associated with remission.

This study is not without limitations. The IMPACT trial enrolled participants 1–4 years of age, so the findings here may not be generalizable to older age groups. This is particularly important as outcome in food immunotherapy may be different in different age groups. (11,12,23,34,35) Another limitation is that only per-protocol participants who completed the DBPCFC at desensitization and/or remission were included in the analyses presented here. As adherence was found to be an important predictor of outcome, including participants that did not meet per-protocol criteria would likely have overestimated the effect size of these results. Real-world adherence is typically lower than what is achieved in clinical trials, so the findings here may be even more pronounced in clinical practice.

Given the inherent risks and burden of pOIT, especially in preschool children, it is crucial to identify which patients are more likely to have a clinical benefit and arm providers, patients, and their families with pOIT response-driven stratification data when deciding whether to pursue pOIT. The work presented here demonstrates for the first time that treatment-emergent variables occurring during OIT treatment – dosing interruptions in OIT during build-up phase and reactions during OIT maintenance influence OIT's efficacy. By carefully preparing patients and caregivers for OIT, developing protocols that support consistent dosing, and monitoring treatment response, clinicians can maximize the benefits of OIT and minimize risks for patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

CoFAR	Consortium for Food Allergy Research
CTD	Cumulative tolerated dose
DBPCFC	Double-blind, placebo-controlled food challenge
IMPACT	Oral Immunotherapy for Induction of Tolerance in Peanut Allergic Children trial
IQR	Interquartile range
ITN	Immune Tolerance Network
ITT	Intention-to-treat
OIT	Oral immunotherapy

pOIT	Peanut oral immunotherapy
SPT	Skin prick test

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Highlights Box

1. What is already known about this topic?

   Most who undergo pOIT achieve desensitization while some achieve remission after discontinuation. A younger age at screening and lower baseline peanut-specific IgE are associated with desensitization and remission.

2. What does this article add to our knowledge?

   This work identifies consecutive missed doses during build-up and dosing-reactions during maintenance as predictors of poor outcomes with peanut oral immunotherapy, and supports shared decision-making about treatment modification during oral immunotherapy.

3. How does this study impact current management guidelines

   By identifying and quantifying clinical correlates associated with successful peanut oral immunotherapy, these findings offer clinicians variables to consider during phases of peanut oral immunotherapy.

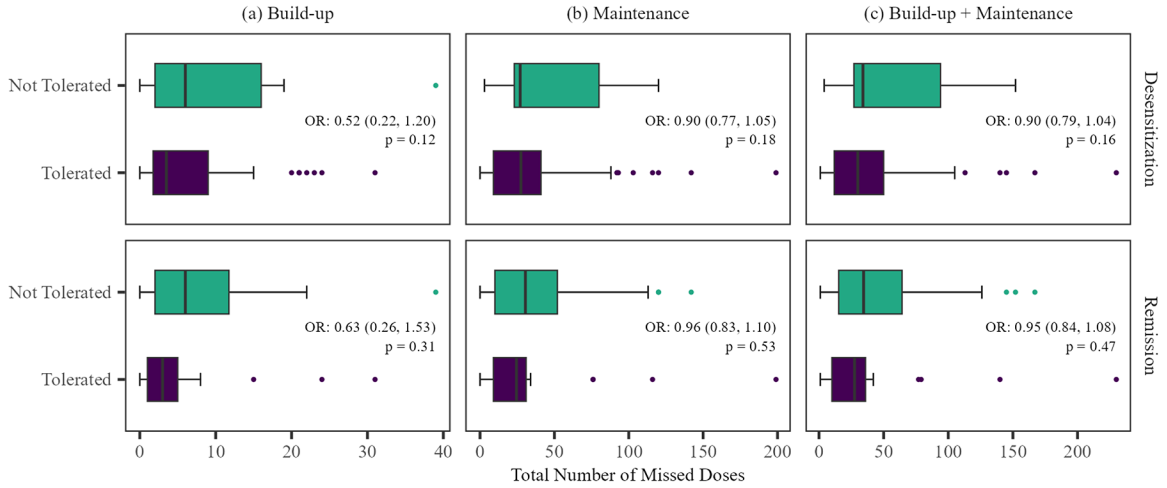

Figure 1.

Total number of missed doses during each study phase

Multivariable logistic regression modeling clinical outcomes at week 134 (desensitization) and week 160 (remission) by the total number of missed doses during the build-up (a), maintenance (b) and build-up and maintenance (c) phases, corrected for baseline age and Ara h2-specific IgE. Purple represents participants who tolerated the DBPCFC; green represents participants who did not. ORs and CIs represent a 10-unit increase in the number of missed doses.

DBPCFC = double blinded placebo-controlled food challenge, OR = odds ratio, CI = confidence interval

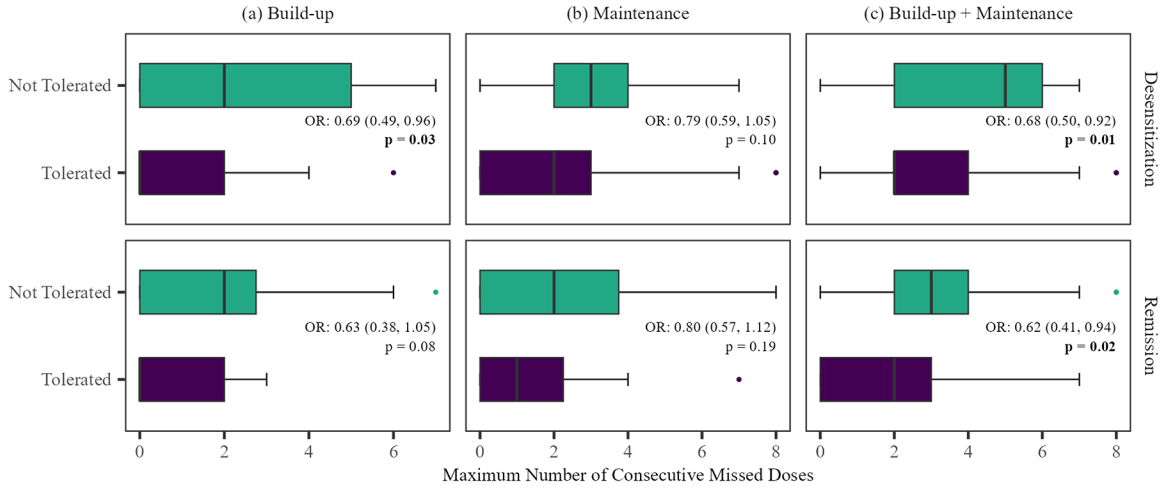

Figure 2.

Maximum number of consecutive missed doses during each study phase

Multivariable logistic regression modeling clinical outcomes at week 134 (desensitization) and week 160 (remission) by the maximum number of consecutive missed doses during the build-up (a), maintenance (b) and build-up and maintenance (c) phases, corrected for baseline age and Ara h2-specific IgE. Purple represents participants who tolerated the DBPCFC; green represents participants who did not. The ORs and CIs represent a 1-unit increase in the maximum number of consecutive missed doses.

DBPCFC = double blinded placebo-controlled food challenge, OR = odds ratio, CI = confidence interval

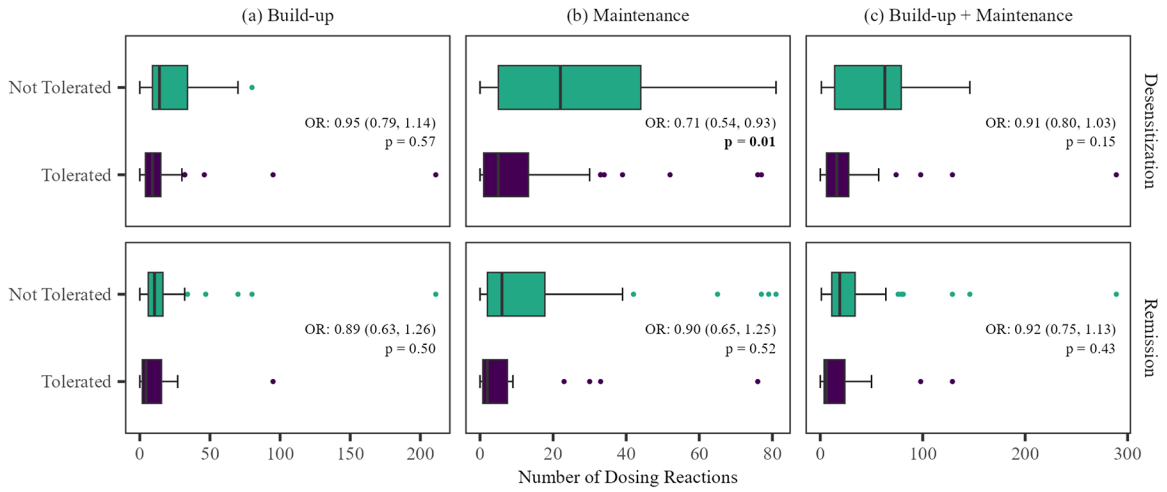

Figure 3.

Total number of dosing-related reactions during each study phase

Multivariable logistic regression modeling clinical outcomes at week 134 (desensitization) and week 160 (remission) by the total number of dosing-related reactions during the build-up (a), maintenance (b) and build-up and maintenance (c) phases, corrected for baseline age and Ara h2-specific IgE. Purple represents participants who tolerated the DBPCFC; green represents participants who did not. The ORs and CIs represent a 10-unit increase in number of dosing-related reactions.

DBPCFC = double blinded placebo-controlled food challenge, OR = odds ratio, CI = confidence interval

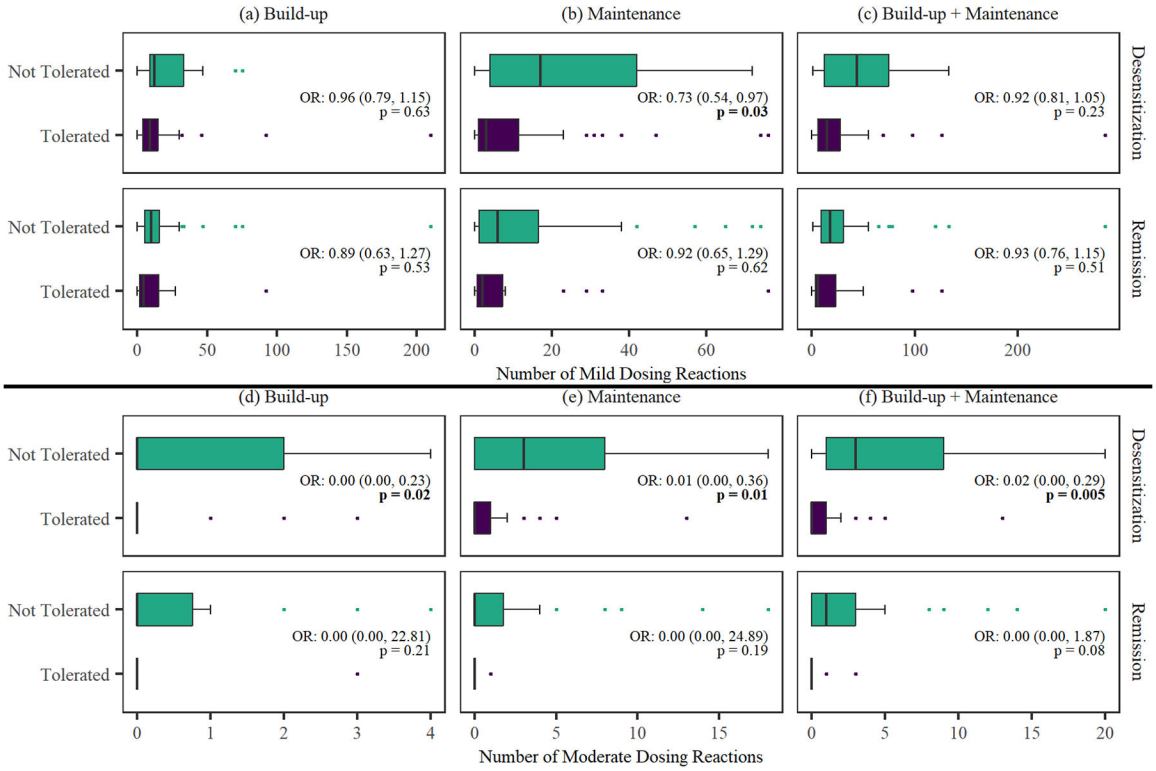

Figure 4.

Total number of dosing-related reaction, by severity, during each study phase of peanut oral immunotherapy

Multivariable logistic regression modeling clinical outcomes at week 134 (desensitization) and week 160 (remission) by the total number of mild dosing-related reactions during the build-up (a), maintenance (b) and build-up and maintenance (c) phases, corrected for baseline age and Ara h2-specific IgE. The total number of moderate dosing reactions during the build-up period (d), maintenance (e) and build-up and maintenance (f) are also shown. Purple represents participants who tolerated the DBPCFC; green represents participants who did not. The ORs and CIs represent a 10-unit increase in the number of mild dosing reactions and a 1-unit increase in the number of moderate dosing reactions.

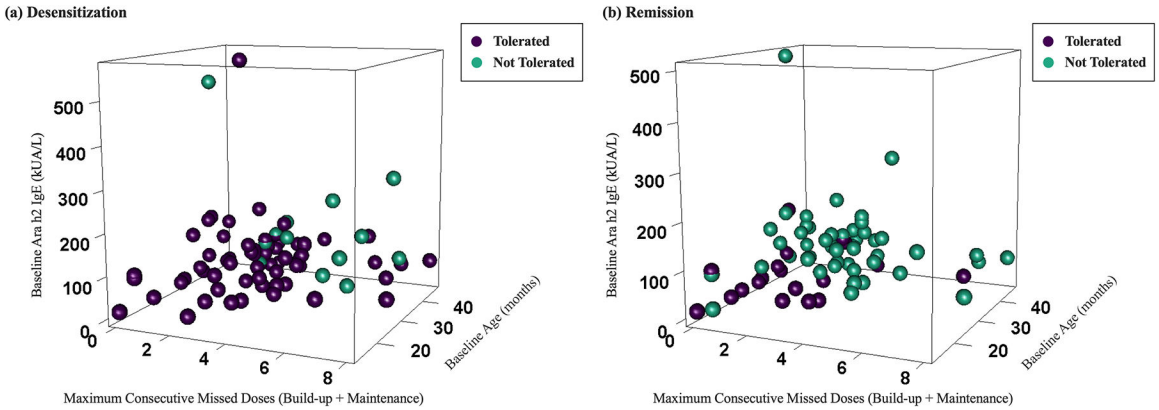

Figure 5.

Distribution of clinical outcomes by consecutive missed doses, age, and baseline Ara h2-specific IgE.

The number of consecutive missed doses, age and baseline Ara h2-specific IgE of participants are plotted in participants who achieved desensitization (a) and remission (b).

Table I.

Demographics and baseline characteristics

	Not Desensitized N = 12	Desensitized N = 49	Remission N = 20	*p*-value*
Baseline Characteristics				
Age at screening, months	40 (39, 42)	39 (33, 45)	31 (24, 40)	0.01[1]
Weight at screening, kg	14.40 (13.88, 15.48)	14.90 (13.80, 16.10)	13.35 (12.28, 14.78)	0.07[1]
Sex				0.49[2]
F	5 (42%)	13 (27%)	7 (35%)	
M	7 (58%)	36 (73%)	13 (65%)	
Race				0.87[2]
Asian	2 (17%)	7 (14%)	4 (20%)	
Black or African American	0 (0%)	1 (2.0%)	0 (0%)	
Mixed Race	3 (25%)	10 (20%)	2 (10%)	
White/Caucasian	7 (58%)	31 (63%)	14 (70%)	
Atopic Dermatitis History				1.00[2]
Yes	10 (83%)	40 (82%)	17 (85%)	
No	2 (17%)	9 (18%)	3 (15%)	
Peanut Allergy History				0.13[2]
History of Peanut Allergy Symptoms	8 (67%)	35 (71%)	9 (45%)	
Never Exposed to Peanut	4 (33%)	14 (29%)	11 (55%)	
History of Other Food Allergies				0.46[3]
No	5 (42%)	25 (51%)	7 (35%)	
Yes	7 (58%)	24 (49%)	13 (65%)	
History of Anaphylaxis to Peanut				1.00[2]
Yes	0 (0%)	0 (0%)	0 (0%)	
No	12 (100%)	49 (100%)	20 (100%)	
Wheal size for skin prick test to peanut at baseline, mm	15.5 (13.9, 20.6)	14.5 (12.0, 17.0)	14.0 (11.5, 18.0)	0.57[1]
Cumulative tolerated dose of masked DBPCFC to peanut at baseline, mg	50 (20, 75)	25 (5, 75)	75 (25, 300)	0.045[1]
Baseline Biomarkers Ara h2-specific IgE at baseline, kUA/L	107 (56, 163)	64 (35, 87)	13 (8, 39)	<0.01[1]
Ara h2-specific IgE/Peanut-specific IgE ratio at baseline, ratio	0.53 (0.44, 0.88)	0.70 (0.42, 1.05)	0.87 (0.67, 1.11)	0.22[1]
Peanut-specific IgE at baseline, kU/L	243 (62, 359)	67 (39, 195)	18 (12, 50)	<0.01[1]
Peanut-specific IgE/Total IgE ratio at baseline, ratio	33 (22, 61)	24 (15, 43)	8 (3, 19)	<0.01[1]
Ara h2-specific IgG4 at baseline, mg/L	0.27 (0.09, 0.36)	0.24 (0.14, 0.41)	0.29 (0.04, 0.52)	0.98[1]
Peanut-specific IgG4 at baseline, mcg/mL	0.84 (0.29, 1.37)	0.56 (0.32, 1.56)	0.73 (0.08, 2.16)	0.86[1]
Peanut-specific IgG4/IgE ratio at baseline, ratio	0.002 (0.001, 0.005)	0.003 (0.001, 0.010)	0.006 (0.002, 0.047)	0.03[1]
Total IgE at baseline, IU/mL	452 (302, 726)	383 (180, 618)	491 (193, 730)	0.53[1]

Note: Unless indicated otherwise, N (%) is presented for categorical variables and Median (IQR) is presented for continuous variables.

*Comparison of each outcome groups' mean or median

[1] Kruskal-Wallis rank sum test

[2] Fisher's exact test

[3] Pearson's Chi-squared test

Table II.

Participant treatment-emergent metrics

	Not Desensitized N = 12	Desensitized N = 49	Remission N = 20	*p*-value*
Dosing Metrics Time to Reach First 2000mg Dose (days)				0.34[1]
Mean (SD)	199 (16)	196 (18)	190 (16)	
Median (IQR)	202 (183 – 205)	193 (182 – 211)	186 (178 – 202)	
Range	181 – 232	167 – 230	169 – 224	
Maximum Maintenance Dose (mg)				0.02[1]
Mean (SD)	1,663 (580)	1,935 (149)	2,000 (0)	
Median (IQR)	2,000 (1,500 – 2,000)	2,000 (2,000 – 2,000)	2,000 (2,000 – 2,000)	
Range	250 – 2,000	1,600 – 2,000	2,000 – 2,000	
Maximum Maintenance Dose (mg), n (%)				0.01[2]
250	1 (8.3%)	0 (0%)	0 (0%)	
900	1 (8.3%)	0 (0%)	0 (0%)	
1200	1 (8.3%)	0 (0%)	0 (0%)	
1600	1 (8.3%)	8 (16%)	0 (0%)	
2000	8 (67%)	41 (84%)	20 (100%)	
Average Daily Maintenance Dose (mg/day)				0.02[1]
Mean (SD)	1,499 (538)	1,831 (175)	1,899 (132)	
Median (IQR)	1,641 (1,374 – 1,934)	1,896 (1,739 – 1,971)	1,934 (1,915 – 1,976)	
Range	249 – 1,992	1,341 – 2,003	1,482 – 2,003	
Duration of Build-up Phase (days)				0.94[1]
Mean (SD)	230 (16)	230 (16)	228 (13)	
Median (IQR)	223 (220 – 236)	225 (217 – 239)	225 (218 – 236)	
Range	215 – 257	207 – 273	210 – 265	
Duration of Maintenance Phase (days)				0.51[1]
Mean (SD)	728.1 (6.3)	729.5 (5.4)	730.1 (5.8)	
Median (IQR)	727.0 (724.0 – 731.3)	728.0 (726.0 – 734.0)	728.0 (727.0 – 730.8)	
Range	721.0 – 740.0	719.0 – 741.0	725.0 – 748.0	

Note: Unless indicated otherwise, N (%) is presented for categorical variables and Median (IQR) is presented for continuous variables.

*Comparison of the outcome groups' mean or median

[1]Kruskal-Wallis rank sum test

[2]Fisher's exact test

Table III.

Reasons for consecutive missed doses

Reason for Consecutive Missed Doses	Events (N = 415)	Participants (N = 64)
Concurrent Illness	211	57 (89.1%)
Participant/Guardian forgot	110	25 (39.1%)
Other	67	23 (35.9%)
Reaction to oral immunotherapy during home dosing	27	12 (18.8%)

[1] n (%) is displayed. Participants are counted only once for each reason. Percentages are based on the number of participants with at least one consecutive missed dose.