Novel baseline predictors of adverse events during oral immunotherapy in children with peanut allergy

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Background: Though peanut oral immunotherapy (OIT) is a promising investigational therapy, its potential is limited by substantial adverse events (AEs), which are relatively understudied.
Objective: A retrospective analysis was conducted, pooling data from 3 pediatric peanut OIT trials, comprising the largest analysis of peanut OIT safety to date.
Methods: We pooled data from 104 children with peanut allergy from 3 peanut OIT studies. We catalogued AEs from parental reports, daily symptom diaries, and dose escalations. We included events that were considered likely related to OIT and identified potential baseline predictors of higher AE rates using generalized linear regression models.
Results: Eighty percent of subjects experienced likely related AEs during OIT (72% during buildup and 47% during maintenance). Of these AEs, over 90% occurred while at home. Approximately 42% of subjects experienced systemic reactions, and 49% experienced gastrointestinal symptoms. Twenty percent of subjects dropped out, with half (10% of the overall group) due to persistent gastrointestinal symptoms. Baseline allergic rhinitis (AR) and peanut SPT wheal size were significant predictors of higher overall AE rates. SPT wheal size predicted increased gastrointestinal AEs, and AR predicted increased systemic reactions. Over the course of OIT, 61% of subjects received treatment for likely related AEs, 59% with antihistamines and 12% with epinephrine.
Conclusions: Peanut OIT is associated with frequent AEs, with rates declining over time, and most graded mild. However, systemic reactions and intolerable gastrointestinal AEs do occur and are significantly associated with AR and peanut SPT wheal size, respectively. Further study is needed of predictive biomarkers and the overall risks and benefits of OIT. (J Allergy Clin Immunol 2017;139:882-8.)

Key words: *Peanut allergy, oral immunotherapy, safety, adverse events*

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Food allergy is a potentially life-threatening condition affecting approximately 3% to 8% of US children.[1-3] With no approved curative therapy, management is restricted to allergen avoidance and supportive measures if symptoms occur.[4,5] A major focus of current research is the development of disease-modifying treatments that modulate the allergic immune response, protecting against accidental exposure. Oral immunotherapy (OIT) for peanut allergy has been shown to successfully desensitize a majority of children with peanut allergy, which has generated excitement about OIT for peanut allergy, but significant concerns remain regarding its safety.[6]

Evaluating the safety profile, however, is complicated by the lack of detailed assessments of safety in larger sample sizes. Furthermore, OIT trials vary widely in both protocols and the methods used to present adverse events (AEs). The few studies focused on safety acknowledge that most reactions are mild or moderate, but risk for systemic reactions requiring epinephrine remains.[7-9]

The goal of our study was to address this knowledge gap by: (1) characterizing the frequencies of OIT-associated AEs and study withdrawals, and (2) identifying baseline characteristics that may identify subjects at higher risk for AEs. Accordingly, we pooled data from 3 trials performed by the same group, examining both AEs in the research unit (ie, staff-observed) and AEs that occur at home, where parents must manage reactions without the support of clinical staff.

METHODS

Study design

In this retrospective analysis, we compiled data from 3 peanut OIT studies: the trial by Jones et al, an uncontrolled pilot study[10,11]; the study by Varshney et al, a randomized, placebo-controlled trial[12]; and the DEVIL (Determining the Efficacy and Value of Immunotherapy on the Likelihood of Peanut Tolerance) study, an ongoing randomized single-center trial. See the Methods section and Table E1 in this article's Online Repository at www.jacionline.org for further details.

Safety data collection

Safety data were collected from 3 sources: records of symptoms occurring during dose escalation at the research unit, symptom diaries of home AEs, and parents' reports of home AEs. All analyses primarily focus on events that were

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Abbreviations used
AE: Adverse event
AR: Allergic rhinitis
ED: Emergency department
EoE: Eosinophilic esophagitis
OIT: Oral immunotherapy

deemed by the investigator as likely related to therapy. See the Methods section in this article's Online Repository for details.

Statistical methods

We computed means, SDs, frequencies, and proportions for all clinical history and immunologic variables. Statistical analyses were conducted using *t*-tests, χ^2 tests, Fisher exact tests, or generalized linear regression modeling (see the Methods section in this article's Online Repository for details). For all analyses (unless specified otherwise), home and research unit AEs were grouped together to best represent the overall risk experienced by participants receiving OIT.

Ethical considerations

All of the trials were conducted in accordance with the principles of the Declaration of Helsinki. For the clinical trials from which these data were generated, ethics approval was obtained from the institutional review boards of the institutions involved. Written informed consent was obtained prior to participation, in accordance with each institution's ethics guidelines for pediatric research.

RESULTS

Subject demographics and participant flow

Of recruited subjects, 94% (104/111) tolerated the initial-day escalation and went on to have OIT administered at home (Fig 1). The remaining 7 included 1 individual who passed the entry challenge, 2 who withdrew prior to initial escalation, and 4 who did not tolerate initial escalation. Of these 4, 2 had difficulties establishing intravenous access in preparation for the protocol, and 2 developed symptoms during the escalation itself (1 with asthma symptoms and 1 with severe abdominal pain and vomiting requiring epinephrine) (Fig 1).

The final study cohort of 104 subjects consisted of a mostly white pediatric population with a slight male predominance (Table I). A majority of subjects had other allergic diseases, including asthma (44%), atopic dermatitis (77%), and allergic rhinitis (AR) (46%). All subjects had a positive peanut SPT result, and 91 subjects (88%) also had an elevated peanut-specific IgE level (≥7 kU/L).

At the time of data extraction, approximately half of the study population had completed the protocol, and a third were still receiving OIT. Twenty-one subjects (20%) withdrew from OIT, 13 did so due to new-onset or worsening symptoms developing on OIT. The remainder withdrew because of logistic difficulty participating in the study. Of the 13 experiencing symptoms, 10 subjects (10% of the overall sample, and 77% of symptomatic withdrawals) dropped out due to new-onset persistent gastrointestinal symptoms (abdominal pain, emesis, and dysphagia), 1 due to worsening asthma, and 2 due to taste aversion. In the 10 who developed gastrointestinal symptoms, the mean presentation time of first gastrointestinal symptom was 17 days (range, 0-74 days); 3 patients were evaluated by means of esophagogastroduodenoscopy, and 2 had findings consistent with eosinophilic esophagitis (EoE).[13]

Characteristics and rates of AEs

Of the 106 subjects who underwent initial dose escalation, 85 (80%) developed at least 1 AE likely related to study treatment, and of the 104 who began buildup OIT, 83 (80%) developed at least 1 AE during their time on therapy (Fig 1). A total of 1077 likely-related AEs were documented among these 83 participants (see Fig E1 in this article's Online Repository at www.jacionline.org). Among all likely related AEs, 75 events (7%), affecting 35 subjects (34%), occurred during dose escalations in the research unit, while the remainder occurred at home (93%). The mean AE rate was 1.7% of dosing days (Table II), with an annualized rate of 3.5. The mean AE rate was higher during the buildup phase than during the maintenance phase of treatment ($P = .005$). The percent of subjects affected by AEs decreased from buildup to maintenance as well ($P < .001$; Table II). This decline in AE rates from buildup to maintenance occurred both among home AEs ($P = .008$) and research-unit events ($P < .001$).

A majority (85%) of the reactions were mild, 15% moderate, and zero severe (Table II). Though these AEs comprised a variety of symptoms, most events involved a combination of skin, upper and lower respiratory, or gastrointestinal symptoms (26%; Fig 2). The most common isolated symptoms were abdominal pain (16%), oral pruritus (16%), nausea/vomiting (9%), and nasal symptoms (8%).

Of all AEs, 113 events (10%) included symptoms indicative of a systemic reaction (as defined in the Methods section of this article's Online Repository), with higher rates during buildup (65 events; 0.3% of dosing days) than in maintenance (48 events; 0.06% of dosing days; $P < .001$). Of the 113 systemic reactions, 110 (97%) occurred at home, while only 3 (<1%) occurred at the research unit. Over the course of therapy, 44 subjects (42%) experienced a systemic reaction, with a rate of 0.3% of dosing days and an annualized rate of 0.37.

Of note, 51 subjects (49%) experienced gastrointestinal events at some time during therapy. Thirty-three percent of AEs (352/1077) included gastrointestinal symptoms, and 26% (281/1077) of AEs involved isolated gastrointestinal symptoms (including abdominal pain, nausea, vomiting, dysphagia, and diarrhea). The annualized rate of gastrointestinal reactions was 1.1.

Predictors of AEs

We found that the presence of AR and the wheal size of the peanut SPT were the only significant predictors of the overall rate of AEs, both before and after adjusting for sex, age, asthma, peanut-specific IgE, and atopic dermatitis (Table III). After controlling for the other variables, the AE rate among subjects with AR was 2.9-fold higher than that in those without AR, and the rates of AEs increased by 1.4-fold for every 5-mm increase in peanut SPT wheal size (Table III). Of note, the unadjusted models for all AEs showed similar results, with both AR and peanut SPT size as significant predictors of AE rate (see Table E2 in this article's Online Repository at www.jacionline.org).

Splitting the models by phase, we found that AR remained significantly associated with higher AE rates during both the buildup and maintenance phases, and the incidence rate ratio associated with AR was increased from 2.1 during buildup to 6.9