Dose-related Allergic Reactions Decrease Over Time During Peanut Oral Immunotherapy in a Large, Randomized, Double-blind, Placebo-controlled, Phase 2 Study

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Introduction

Oral immunotherapy (OIT) is currently under investigation for the treatment of peanut allergy and its long-term safety is unknown. We evaluated OIT-related adverse events (AEs) during multi-year peanut OIT to better understand the long-term safety of OIT.

Methods

120 participants aged 7-55 years with confirmed peanut allergy were enrolled in a double-blind, placebo-controlled, phase 2 study of peanut OIT. Participants were randomized to escalate to and maintain 4000 mg peanut protein (n=95) or placebo (n=25) daily over 104 weeks. 60 then discontinued (peanut-0) while 35 received 300 mg daily—about one peanut kernel—(peanut-300). Double-blind, placebo-controlled food challenges (DBPCFCs) to 4 g peanut protein were conducted at baseline, week 104, and every 13 weeks thereafter for one year (**Figure 1**).
The per-person AE rate was calculated by dividing the number of AEs per year by the number of doses taken each year. Differences in per-person median AE rates between groups of interest were evaluated using Kruskal-Wallis rank sum test. To determine whether baseline characteristics were associated with adverse events (AEs), linear regression models were fit to the percentages of doses at which an AE occurred as a function of each baseline characteristic, adjusting for treatment.

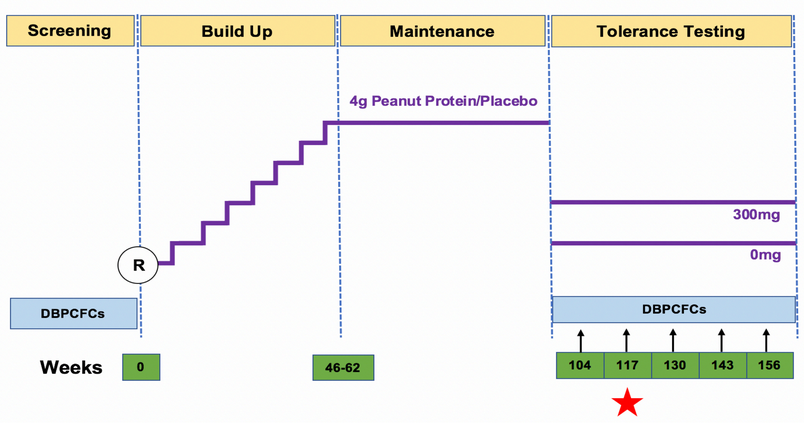

Figure 1: Study Design, star denotes primary endpoint

Results

The overall AE rate significantly decreased over study years in both arms (*P*<0.0001, **Figure 2**). The AE rate decreased from 0.50 in year 1 to 0.14 in year 2 (*P*<0.0001), with a significantly greater reduction from year 1 to year 2 in the peanut arm compared to placebo (-0.22 vs 0.00, *P*=0.0043).

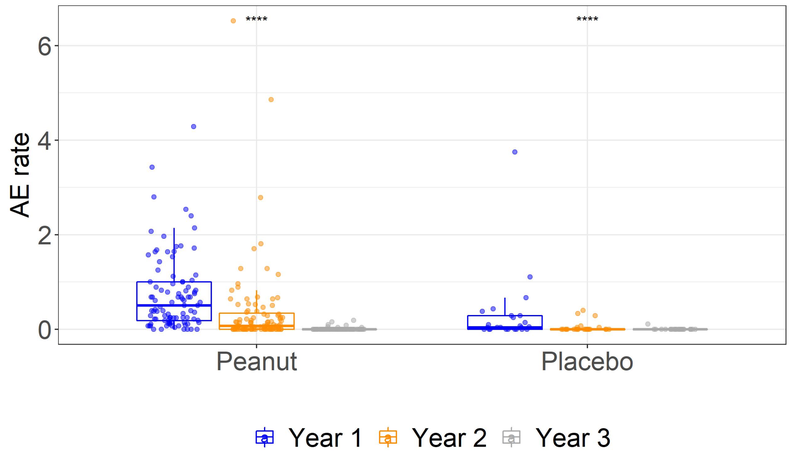

Figure 2. AE rate changes over study year by treatment group. ****P*<0.0001.

Baseline Characteristic	Estimate	P-value	Q-value
Age	-0.01	0.71	0.95
Male	-0.34	0.43	0.75
Asian	-0.14	0.76	0.95
Multi-racial	0.83	0.22	0.55
History of Asthma	0.48	0.26	0.57
History of atopic dermatitis	-0.38	0.42	0.75
History of allergic rhinitis	0.08	0.86	0.95
BMI	-0.03	0.45	0.75
Number of doctor diagnosed food allergies	-0.01	0.83	0.95
Age at diagnosis of peanut allergy	-0.11	0.33	0.65
Time since diagnosis of peanut allergy	0	0.87	0.95
Cumulative tolerated dose	0	0.51	0.81
%CD63high area under peanut dose curve	0	0.78	0.95
Peanut skin prick test	-0.05	0.17	0.51
Total serum IgE (log10)	-0.04	0.92	0.95
Peanut sIgE/Total IgE (log10)	0.93	0.002	0.02
Peanut sIgE (log10)	0.67	0.008	0.05
Ara h 1 IgE (log10)	0.38	0.001	0.02
Ara h 2 IgE (log10)	0.59	0.002	0.02
Ara h 3 IgE (log10)	0.25	0.03	0.15
Ara h 8 IgE (log10)	0.05	0.69	0.95
Ara h 9 IgE (log10)	0.02	0.89	0.95
Ara h 1 IgE/Peanut sIgE (log10)	0.65	0.003	0.02
Ara h 2 IgE/Peanut sIgE (log10)	0.86	0.03	0.15
Ara h 3 IgE/Peanut sIgE (log10)	0.46	0.06	0.21
Ara h 8 IgE/Peanut sIgE (log10)	-0.06	0.77	0.95
Ara h 9 IgE/Peanut sIgE (log10)	-0.34	0.22	0.55
Peanut sIgG4 (log10)	0.34	0.27	0.57
Peanut sIgG4/Peanut sIgE (log10)	-0.56	0.06	0.21

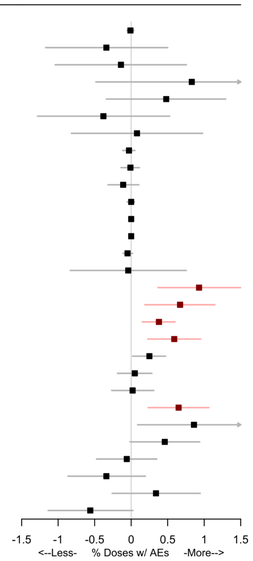

Figure 3. Baseline characteristics and their association with the percentage of doses in which an adverse event occurred (% doses w/AEs) from study start up to week 117 in the ITT population. An estimate above 0 (gray line) denotes an association with more % doses w/AEs, while an estimate below 0 denotes an association with less. Q-value is the FDR-adjusted P-value.

Results cont.

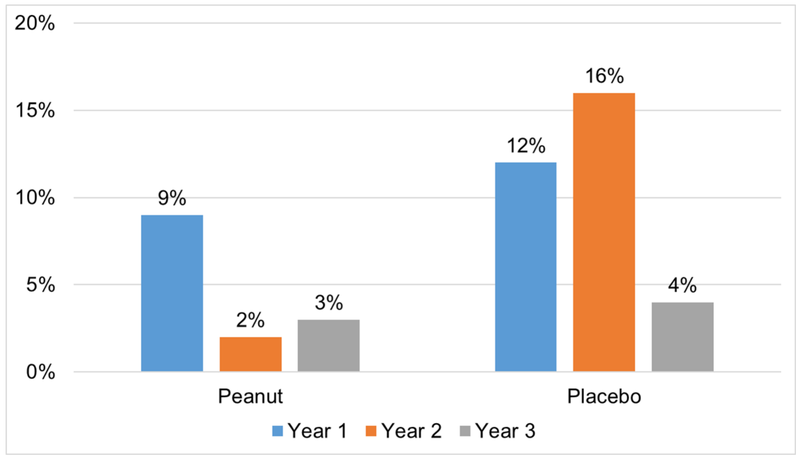

Figure 4. Participants reporting AEs related to accidental peanut ingestion decreased between year 1 (9%) and 2 (2%) in the peanut arm (Fisher's exact test *P*=0.06), while placebo did not change (12% to 16%, *P*=1.00). There was no significant difference between year 2 and year 3 in both arms.

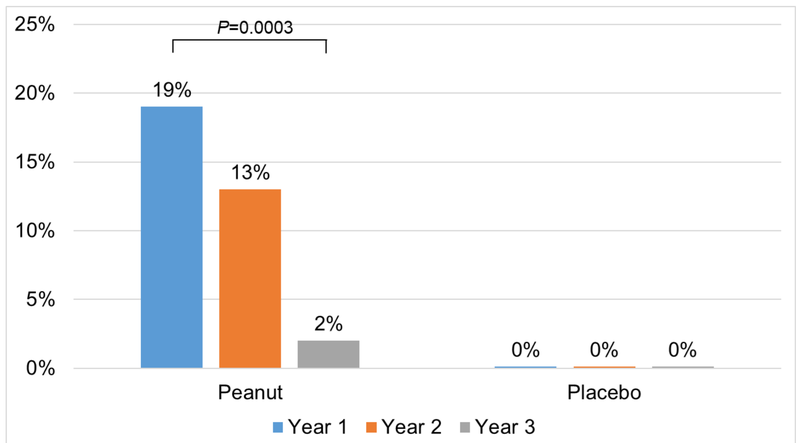

Figure 5. The use of epinephrine to treat allergic reactions declined within the peanut arms with longer duration on peanut (19% year 1, 13% year 2, 2% year 3, *P*=0.0003).

Conclusions/ Future Directions

In this large, phase 2 study, we are able to follow safety signals over 2-3 years of dosing. Our findings show that the safety profile of peanut OIT improves as time on therapy increases.

Funding

This work was supported by NIH (U19AI10420906) and by the Sean N. Parker Center for Allergy and Asthma Research at Stanford University.