

Letter to the Editor

Sublingual versus oral immunotherapy for peanut-allergic children: A retrospective comparison*To the Editor:*

There has been considerable recent interest in developing therapies for food allergy, an increasingly common and highly morbid disorder for which strict dietary elimination and ready access to epinephrine remain the standard of care.¹ While both oral immunotherapy (OIT)²⁻⁴ and sublingual immunotherapy (SLIT)⁵ have been shown to induce clinical desensitization to foods (reviewed in Narisety and Keet⁶), no head-to-head comparative analysis of the 2 treatments has been published.

We conducted a retrospective study of 2 previously published protocols for peanut allergy.^{2,3} This new analysis includes additional subjects, compares the 12-month oral food challenge outcomes, and extends analysis of immunologic parameters out to 24 months. Eligible peanut-allergic subjects were recruited into 1 of 2 concurrent clinical trials: OIT (maintenance dose of 4000 mg/day and cumulative double-blind, placebo-controlled challenge [DBPCFC] dose of 5000 mg) or SLIT, (2 mg/day and 2500 mg, respectively) (all quantities refer to peanut protein). Although the optimal immunotherapy dose remains unknown, the doses chosen in these trials were based on preliminary data from pilot studies. Of note, unique properties of the oral mucosal immune response are hypothesized to account for SLIT's efficacy at log-fold lower doses (reviewed in Novak et al⁷). Both trials utilized randomized, double-blind, placebo-controlled designs. Mechanistic studies were performed longitudinally as previously described by using blood drawn from subjects within 24 hours of their last immunotherapy dose.^{2,3} At 12 months, subjects underwent DBPCFC to assess clinical desensitization; OIT subjects received a maximal 5000 mg cumulative protein dose, and for safety reasons, SLIT challenges were limited to 2500 mg (see [Tables E1 and E2](#) in this article's Online Repository at www.jacionline.org). We compared laboratory data between OIT and SLIT at baseline, 12 months, and 24 months, as well as DBPCFC pass/fail outcomes by using the Wilcoxon signed rank test (STATA 12, College Station, Tex) and Mann-Whitney *U* test (GraphPad Prism, La Jolla, Calif).

Twenty-three subjects on OIT and 27 subjects on SLIT were evaluated after receiving 2 years of treatment ([Table I](#)). We did not undertake a formal comparison of safety parameters between the 2 studies, and upcoming interval reports of each study will include these data. However, there were no serious adverse events reported in either study. No SLIT and 2 OIT subjects (1 active, 1 placebo) required 4 total doses of epinephrine for dose-related reactions. At baseline, the peanut-specific IgE level was similar between OIT and SLIT subjects ([Fig 1, A](#)). Twelve months of treatment led to higher median peanut-specific IgE levels in the OIT group than in the SLIT group (204.5 kU/L vs 66.7 kU/L, *P* = .0382); however, levels were not significantly different between the groups at 24 months ([Fig 1, A](#)). While peanut-specific IgG₄ level increased over time in both groups ([Fig 1, B](#)), the effect was greater with OIT at 12 (20.1 mg/L vs 3.1 mg/L) and 24 months (20.3 mg/L vs 7.9 mg/L, *P* < .001). Although decreased in both groups, median peanut-specific IgE/IgG₄ ratios were significantly

TABLE I. Baseline subject characteristics

	Peanut OIT	Peanut SLIT	<i>P</i> value
No. evaluated	23	27	
Median age at enrollment (y) (range)	5.3 (3-10)	6.3 (2-11)	.45
Males, n (%)	13 (57)	21 (78)	.14
Race	21 White 2 Black	26 White 1 Asian	.59
Median peanut-specific IgE (kU/L), range	58.5 (12-985)	61.7 (8.5-1636)	.67
Median skin prick test (mm), range	14.5 (7-26)	11.5 (3.5-23.5)	.04
Asthma, n (%)	13 (57)	14 (52)	.78
Atopic dermatitis, n (%)	17 (74)	21 (78)	>.99
Allergic rhinitis, n (%)	16 (70)	19 (71)	>.99
Other food allergy, n (%)	14 (61)	9 (33)	.09

lower at 12 and 24 months for subjects receiving OIT ([Fig 1, C](#)). Thirty-four subjects (14 OIT, 20 SLIT) had basophil activation assessed by CD63 upregulation at baseline and 12 months. After 12 months, a significantly lower percentage of CD63⁺ basophils was found in the OIT group than in the SLIT group when stimulated with 10⁰ (median 5.90% vs 21.50%) and 10⁻¹ µg/mL (median 6.34% vs 30.75%) crude peanut extract (*P* < .01). No between-group difference was seen after stimulation with weaker dilutions of 10⁻² and 10⁻³ µg/mL crude peanut extract. Too few samples were obtained at 24 months to perform an analysis.

Eighteen subjects on OIT and 27 subjects on SLIT underwent 12-month desensitization DBPCFCs, results of which are shown in [Fig 1, D](#). Despite differences in DBPCFC protocols, SLIT subjects reacted at lower eliciting dose thresholds. A Fisher exact test was used to calculate the difference in proportions and the relative risk for passing or failing the DBPCFC according to the treatment group. The difference in proportions was statistically significant (*P* = .002), with OIT-treated subjects 3 times more likely than SLIT-treated subjects (relative risk = 3.00, 95% CI, 1.64-5.49) to pass the 12-month desensitization DBPCFC.

In an attempt to identify candidate biomarkers, we combined all SLIT and OIT subjects and then categorized them by "pass" or "fail" on the basis of their ability to complete the DBPCFC without symptoms. Consistent with other studies, subjects passing the 12-month desensitization DBPCFC tended to have lower baseline peanut-specific IgE levels (34.6 kU/L vs 167 kU/L, *P* = .0575) ([Fig 1, E](#)). Peanut-specific IgG₄ level was increased by 27-fold in the "pass" group compared with a 6.5-fold increase in the "fail" group (*P* = .01; [Fig 1, F](#)). Interestingly, the percentage of CD63⁺ basophils was significantly lower at 12 months in the "pass" group compared with the "fail" group when stimulated with 10⁰ (median 5.90% vs 21.50%) and 10⁻¹ µg/mL (median 6.34% vs 34.75%) crude peanut extract (*P* < .01). Again, no differences were seen between groups after stimulation with weaker dilutions. Skin prick tests decreased over time in all subjects. Wheal size, serum peanut-specific IgA and peanut-specific IgG, and CD4⁺CD25⁺FoxP3⁺ T-regulatory cells were not significantly different between the OIT and SLIT groups or the "pass" and "fail" groups.

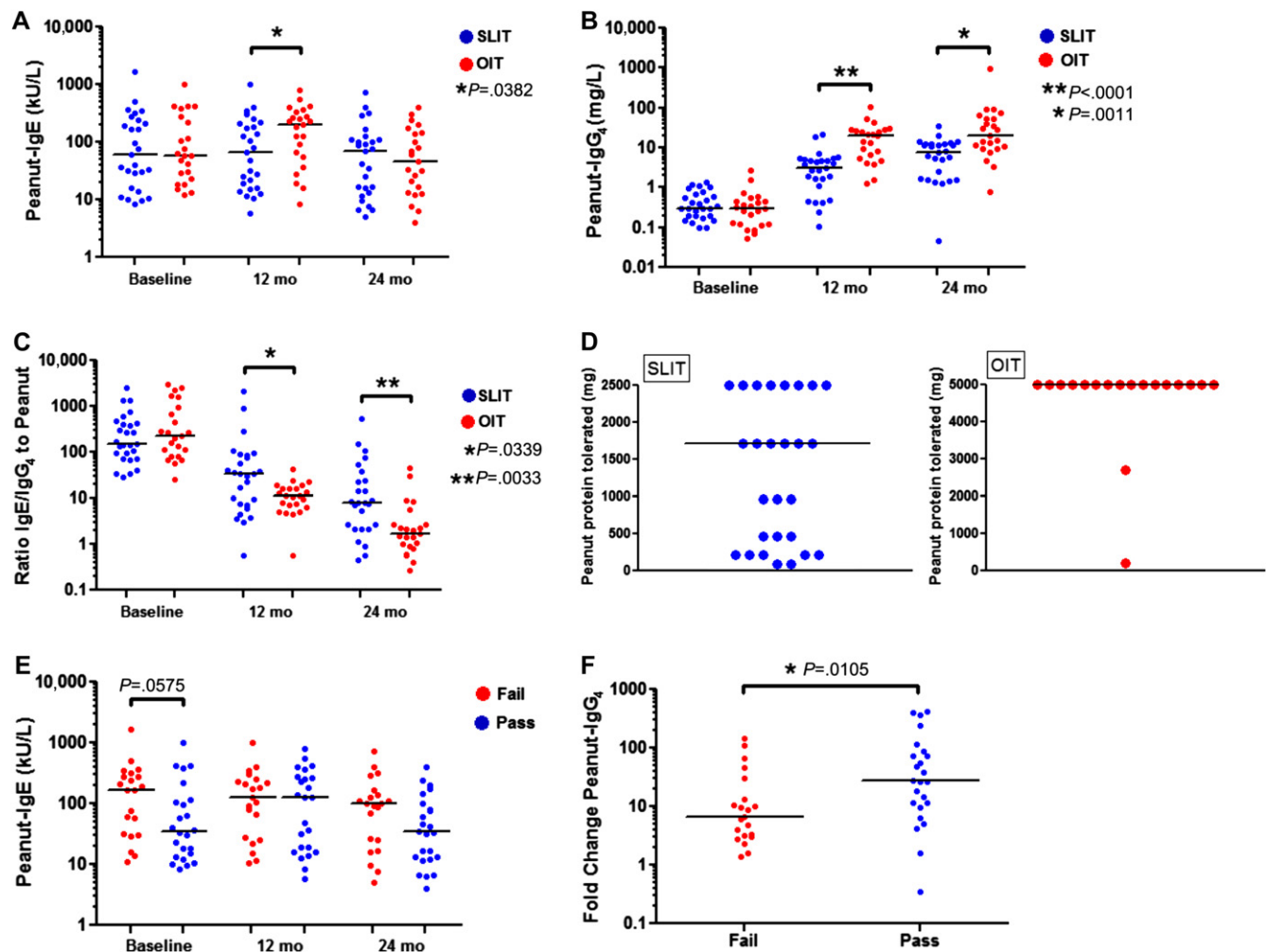


FIG 1. A and B, Change in serum peanut-IgE and peanut-IgG₄ (SLIT/OIT). C, IgE/IgG₄ ratio to peanut (SLIT/OIT). D, Cumulative amount tolerated during DBPCFC (SLIT/OIT). E, Serum peanut-IgE (pass/fail). F, Fold change in serum peanut-IgG₄ from baseline to 12 months (pass/fail). Scatter plots show individual data with a line designating the median.

In summary, our results suggest that after 2 years of treatment, OIT produces greater immunologic changes than SLIT in peanut-allergic children. Specifically, peanut OIT resulted in greater changes in peanut-specific IgE, IgG₄, and IgE/IgG₄ ratio as well as basophil activation. In addition, eliciting dose thresholds were lower and more variable during DBPCFC at 12 months in SLIT-treated subjects than in OIT-treated subjects. Subjects who passed the DBPCFC tended to have lower baseline peanut-IgE levels, in addition to a larger fold change in peanut-IgG₄ and less basophil activation at 12 months. The major limitation of this study is that it was not a randomized prospective study designed to directly compare the 2 modalities with a uniform protocol and consecutive enrollment. It is important to also note that interim clinical end points measured after only 12 months of immunotherapy likely do not provide a full assessment of the efficacy of either method. Further research is needed to determine the optimal length of treatment, dose, and ideal immunotherapy candidate for each modality.

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TABLE E1. Dosing schedule for OIT DBPCFC

Dose	Interval (min)	Individual dose (mg flour)*	Cumulative dose (g flour)
1	—	5	0.0050
2	20	15	0.0200
3	20	50	0.0700
4	20	100	0.1700
5	20	250	0.4200
6	20	500	0.9200
7	20	1000	1.9200
8	20	1500	3.4200
9	20	2000	5.4200
10	20	4000	9.4200

*Protein content of flour is 50% by dry weight.

TABLE E2. Dosing schedule for SLIT DBPCFC

Dose	Interval (min)	Individual dose (mg flour)*	Cumulative dose (g flour)
1	—	170	0.170
2	20	250	0.420
3	20	500	0.920
4	20	1000	1.920
5	20	1500	3.420
6	20	1580	5.000

*Protein content of flour is 50% by dry weight.