Clinical Communications

Modified peanut oral immunotherapy protocol safely and effectively induces desensitization

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Clinical Implications

- The build-up phase for peanut oral immunotherapy may be shortened by establishing the starting dose based on the eliciting dose threshold and building up to a 2 g maintenance dose. This approach is safe and effective.

TO THE EDITOR:

Peanut oral immunotherapy (OIT) has been shown to effectively induce desensitization in the majority of peanut-allergic individuals who receive therapy.[1-3] However, questions exist regarding its safety and the optimal dose of peanut protein to administer. Studied maintenance doses range from 800 mg daily[3] to 4000 mg daily.[2] Side effects, which are typically mild, are most often seen during the build-up phase of therapy[2,4,5]; therefore, we hypothesized that minimizing time to maintenance dosing may be favorable for the safety of individuals over the course of the therapy. We designed an unblinded peanut OIT pilot study that shortened time to maintenance by incorporating (1) a modified entry dose protocol and (2) a 2000 mg maintenance dose. Desensitization endpoints comparable to previously published protocols utilizing a 4000 mg maintenance dose were used for comparison.[1,2]

Inclusion and exclusion criteria are outlined in Table E1 (available in this article's Online Repository at www.jaci-inpractice.org) and required objective symptoms of allergic reactivity within 60 minutes of peanut ingestion during a double-blind, placebo-controlled food challenge (DBPCFC) to 2000 mg of peanut protein.

Dose initiation was performed as outlined in Table I, utilizing lightly roasted peanut flour (partially defatted 12% fat; Golden Peanut Co., Alpharetta, Ga; 2 g flour = 1 g peanut protein). A modified entry dose was based on the threshold dose of reactivity. Build-up dosing occurred approximately every 2 weeks. After dose initiation, doses were increased as previously described.[2] A 5000 mg DBPCFC was performed after approximately 4 months of maintenance dosing (median 105 days, range 83 to 181 days). Subjects were instructed to resume 2000 mg daily dosing after the DBPCFC.

Titrated skin prick tests (SPTs) were performed every 6 months with peanut extract (Greer Laboratories, Lenoir, NC). Peanut-specific IgE and IgG4 levels were measured using the ImmunoCAP 100 instrument (Phadia AB, Uppsala, Sweden) according to the manufacturer's instructions. Approval for this study was obtained through the University of Texas Southwestern Institutional Review Board.

Differences in the values over time compared with baseline were analyzed by using the Wilcoxon rank-sum tests (GraphPad Prism version 6.00 for Windows, GraphPad Software, La Jolla, Calif) on matched data. P values $<.05$ were considered significant.

Twelve subjects were screened and 11 met entry criteria (see Table E2 in this article's Online Repository at www.jaci-inpractice.org). Of the 11 subjects, 9 were able to safely ingest the 2000 mg daily maintenance dose. Details regarding the 2 subjects unable to achieve maintenance are included in Table E2. The median time to maintenance was 41 weeks (28-48 weeks) (Table E2). The most common reason to delay up-dosing was related to convenience (eg, inability to miss school, study staff vacation, etc.). Adjusting the time to maintenance with removal of convenience factors yields a median time to maintenance of 36 weeks (26-45 weeks).

All 9 subjects who achieved maintenance dosing passed the 5000 mg peanut DBPCFC (Figure 1). Three subjects experienced transient symptoms during the challenge, which were not deemed significant enough to discontinue the challenge. From entry to the 5000 mg DBPCFC, 3265 total doses were administered. Only 7.9% of doses (264/3265) were associated with a reported side effect. All side effects were mild except for 2 severe reactions (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). The majority of reactions, 94% (249/264), occurred during the build-up phase. The most common complaints during build-up included skin reactions, followed by throat clearing and sneezing (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

The skin prick test wheal diameter decreased significantly in all subjects after 6 months of therapy (see Figure E2A in this article's Online Repository at www.jaci-inpractice.org). Peanut-specific IgE, IgG4, and IgE/IgG4 changed significantly after 6 weeks of therapy (see Figure E2B-D in this article's Online Repository at www.jaci-inpractice.org), similar to findings from investigators using other protocols.[2]

Secondary to our modified entry dose protocol with a lower maintenance dose, our subjects were able to achieve maintenance dosing in a shorter time frame, and with comparable levels of desensitization and similar effects on the immune response as reported by previous investigators.[1,2] Making head-to-head comparisons between existing peanut OIT studies is difficult secondary to the varied approaches investigators have taken. Begin et al recently reported successful acquisition of maintenance dosing by an average of 18 weeks with 4000 mg dosing per allergen for multiple allergen OIT; however, omalizumab is given adjunctively during up-dosing.[6] Our up-dosing regimen was longer, but we did not use omalizumab. Our reaction rate was similar (5.3% [Begin] vs 7.9% [Bird]) without the protective benefits of omalizumab.

We have now shown that 9/9 children who received a 2000 mg maintenance dose were able to pass a 5000 mg challenge with 6/9 (66%) having no symptoms during the challenge, and they were able to achieve maintenance dosing in a median time of 41 weeks. Because of differences in time receiving maintenance, total time on therapy, and differences in the amount of protein given during the desensitization challenge, we cannot directly compare our study with the recent study by Anagnostou et al.[3] It

TABLE I. Entry food challenge protocol and starting OIT dose based on the highest tolerated dose

Dose no.	Approximate dose weight (mg) (peanut protein)	Cumulative dose weight (mg) (peanut protein)	Starting dose of OIT (mg)
1	1	1	0.1 (perform desensitization with initial dose escalation to 6 mg)
2	5	6	
3	15	21	
4	54	75	12.5
5	75	150	25
6	100	250	50
7	250	500	150
8	500	1000	300
9	1000	2000	750

OIT, oral immunotherapy.

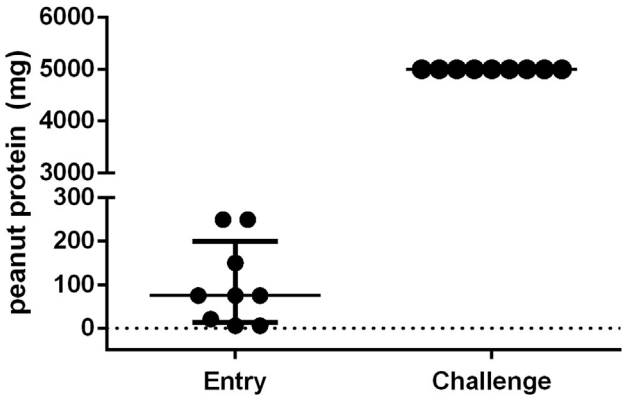

FIGURE 1. Subjects who completed the desensitization challenge (n = 9) tolerated a median dose of 75 mg of peanut protein at study entry and 5 g of peanut protein approximately 4 months after ingesting 2 g of peanut protein daily ($P < .05$). Circles represent individual subjects. Horizontal lines represent the median and interquartile range.

seems reasonable, however, to report that the data from our group appear as efficacious as the report by Varshney et al,[2] with our subjects receiving a lower daily maintenance dose and able to safely ingest equitable amounts of peanut protein, with maintenance dosing achieved in a shorter time frame.

When considering OIT as a practical approach to treatment for peanut allergy, our protocol offers several distinct advantages. First, in our experience, subjects often have difficulty ingesting a large dose of peanut flour, and a lower maintenance dose is better tolerated. It is also important to note that a 2000 mg dosing regimen induced similar immunologic effects regarding desensitization. Secondly, dose initiation without an initial dose escalation day, as reported in previous protocols, did not increase the reaction rate in our small cohort. As we continue advancing our knowledge regarding OIT, it is important to consider which aspects of the build-up phase are necessary when and if OIT becomes acceptable in common practice for treatment of food allergy.

Study strengths include validation of peanut allergy with an entry DBPCFC, shortened time to maintenance with an equitable safety profile, and immunologic changes reflective of the development of a desensitized state. Interpretability is limited by the small sample size; however, this is a pilot study. We will continue to follow our cohort to measure the development of tolerance and to provide preliminary data on any effect our lower dosing regimen may have on the potential development of tolerance.

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Conflicts of interest: J. A. Bird has received research support from the Dedman Family in Clinical Care Funding and Food Allergy Research and Education; has received consultancy fees from SRA International; has received lecture fees from Nutricia; has participated in epicutaneous patch immunotherapy for peanut multicentered trial for DBV Technologies; and has participated in peanut oral immunotherapy multicentered trial for Allergen Research Corporation. M. Feldman has received consultancy fees from Patient Point, and is employed by the Dallas Allergy & Asthma Center. L. S. Brown has received fees from UT Southwestern for statistical analysis, and is employed by Parkland Hospital. M. Kulis is employed by the University of North Carolina at Chapel Hill, and has received research support from the National Institutes of Health (NIH). A. W. Burks was on the Merck Board; has received consultancy fees from Dow AgroSciences, Exploramed Development, GLG Research, McNeill Nutritionals, Merck, Novartis Pharma, Regeneron Pharmaceuticals, Unilever, ActoGeniX, SRA International, Genentech, Sanofi US Services, and Nutricia North America; is employed by the University of North Carolina; has received research support from the NIH, Hycor Biomedical, and Allergen Research Corporation; has received lecture fees from Mylan Specialty; and has stock/stock options in Allertein and Mastcell Pharmaceuticals. M. Gill has received research and travel support from the NIH/National Institute of Allergy and Infectious Diseases. The rest of the authors declare that they have no relevant conflicts.

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