Sustained unresponsiveness to peanut in subjects who have completed peanut oral immunotherapy

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Background: Although peanut oral immunotherapy (OIT) has been conclusively shown to cause desensitization, it is currently unknown whether clinical protection persists after stopping therapy.

Objective: Our primary objective was to determine whether peanut OIT can induce sustained unresponsiveness after withdrawal of OIT.

Methods: We conducted a pilot clinical trial of peanut OIT at 2 US centers. Subjects age 1 to 16 years were recruited and treated for up to 5 years with peanut OIT. The protocol was modified over time to permit dose increases to a maximum of 4000 mg/d peanut protein. Blood was collected at multiple time points. Clinical end points were measured with 5000-mg double-blinded, placebo-controlled food challenges once specific criteria were met.

Results: Of the 39 subjects originally enrolled, 24 completed the protocol and had evaluable outcomes. Twelve (50%) of 24 successfully passed a challenge 1 month after stopping OIT and achieved sustained unresponsiveness. Peanut was added to the diet. At baseline and the time of challenge, such subjects had smaller skin test results, as well as lower IgE levels specific for peanut, Ara h 1, and Ara h 2 and lower ratios of peanut-specific IgE/total IgE compared with subjects not passing. There were no differences in peanut IgG_4 levels or functional activity at the end of the study.

Conclusions: This is the first demonstration of sustained unresponsiveness after peanut OIT, occurring in half of subjects treated for up to 5 years. OIT favorably modified the peanut-specific immune response in all subjects completing the protocol. Smaller skin test results and lower allergen-specific IgE levels were predictive of successful outcome. (J Allergy Clin Immunol 2014;133:468-75.)

Key words: *Peanut allergy, oral immunotherapy, desensitization, tolerance, sustained unresponsiveness*

Food allergy is the leading cause of anaphylaxis in children, and in the last 20 years, it has become an increasingly prevalent public health problem with adverse medical, psychosocial, and economic effects.[1-5] This is especially true for peanut allergy, which carries a high risk of severe reactions[6,7] and is typically a lifelong disorder.[8,9] Presently, the standard of care for food allergy is strict dietary allergen elimination and ready access to emergency medications. Consensus National Institutes of Health guidelines recommend against the current use of interventional therapies.[2]

However, recent trials of oral immunotherapy (OIT) have demonstrated progress toward an active treatment approach for food allergy.[10-15] In a preliminary report from an uncontrolled pilot study of peanut OIT in children, our group demonstrated that successful clinical desensitization occurred in 27 (93%) of 29 subjects completing more than 8 months of therapy and was associated with relevant mechanistic changes in the peanut-specific immune response.[13] Subsequently, a randomized placebo-controlled trial conclusively demonstrated desensitization and immunomodulation, validating the pilot work and supporting the efficacy of OIT in patients with peanut allergy.[15] Other mechanistic studies have shown that peanut OIT complexly

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Abbreviations used
DOFC: Desensitization oral food challenge
FAB: Facilitated antigen binding
OFC: Oral food challenge
OIT: Oral immunotherapy
SOFC: Sustained unresponsiveness oral food challenge
TF: Treatment failure
TS: Treatment success

modifies the IgE and IgG_4 responses to the linear epitopes from the major peanut allergens Ara h 1, 2, and 3[16] and induces basophil hyporesponsiveness during treatment.[17] Collectively, these results support the idea that the immunomodulatory effects of OIT are similar to accepted forms of immunotherapy that have been proved to be disease modifying in patients with venom anaphylaxis and respiratory allergy.[18-20]

Yet only 1 trial to date has conclusively demonstrated that OIT is disease modifying by using egg white powder in subjects with egg allergy.[21] The term "sustained unresponsiveness" was introduced in this landmark study, describing the ability of a subject to pass an oral food challenge (OFC) after stopping OIT and successfully introduce a previously allergenic food into the diet *ad libitum*. Whereas egg allergy is commonly outgrown, this is uncommon for peanut allergy, and sustained unresponsiveness to peanut has not previously been shown.

We sought to determine, in the same peanut-allergic cohort in whom desensitization was previously reported,[13] whether long-term treatment with OIT would result in sustained unresponsiveness to peanut and to identify the clinical and immunologic parameters associated with this state.

METHODS

Subject recruitment

This trial was conducted in accordance with the principles of the Declaration of Helsinki. Ethics approval was obtained through the Institutional Review Boards at Duke University Medical Center and the University of Arkansas for Medical Sciences. Written informed consent was obtained before study participation in accordance with each institution's ethics guidelines for research in children. Subjects (age, 1-16 years) were recruited from the allergy and immunology clinics or surrounding community physicians' offices at both sites. An interim analysis of this cohort of subjects was previously published[13]; the end-of-study results of the same clinical trial are presented here.

OIT protocol

Details of subject selection and the peanut OIT protocol have been previously published[13] and are available in the Methods section in this article's Online Repository at www.jacionline.org. Briefly, OIT was administered in an open-label fashion to subjects with peanut allergy daily in 3 phases (ie, initial-day escalation, build-up, and maintenance), which continued until subjects met eligibility for end point assessment, as described below. For the duration of the study, subjects strictly avoided all peanut except for that provided in the dose of their study product.

Clinical end points

Subjects in this study underwent at least 3 OFCs. The first, which was previously reported,[13] was an open OFC to 3900 mg of peanut protein conducted shortly after reaching the maintenance dose. In the current study qualifying subjects from the previous report were evaluated with 2 double-blind, placebo-controlled food challenges to a total of 5000 mg of peanut protein performed 4 weeks apart. Details of these challenges have been previously published.[15] The first of these challenges (referred to in the figures as desensitization oral food challenge [DOFC]) was performed to assess reactivity while receiving treatment, and OIT was stopped if this double-blind, placebo-controlled food challenge was passed. The next challenge (referred to in the figures as sustained unresponsiveness oral food challenge [SOFC]) was conducted 4 weeks after stopping OIT and assessed the primary end point called sustained unresponsiveness, which we operationally defined as the ability to asymptomatically consume all of the challenge material and then an open oral feeding of one serving (eg, 8,000-10,000 mg) of peanut butter afterward on the same day. Subjects passing the SOFC were classified as treatment successes (TSs), and those with convincing allergic symptoms during their final SOFC or open feeding were classified as treatment failures (TFs). The criteria for the timing of the assessment of sustained unresponsiveness varied as the study progressed. The initial protocol called for SOFC once peanut IgE levels were less than 2 kU/L. We subsequently amended the protocol to offer SOFCs to subjects with a peanut IgE level of less than 15 kU/L, a peanut skin prick test response of less than 5 mm, and no peanut-related reactions in the previous 6 months. Because of the exploratory nature of this pilot study, if subjects failed the SOFC during these first 2 phases of evaluation, they resumed OIT. The final phase of assessment for sustained unresponsiveness occurred in all remaining subjects who underwent SOFC at the completion of 5 years of OIT, regardless of their immune parameters. TSs were advised to incorporate peanut into the diet *ad libitum* at least several days per week. The day after the final SOFC, TFs were restarted on a predetermined amount of a peanut-containing food daily and are being followed.

Clinical and mechanistic studies

Skin prick tests were performed in standard clinical fashion throughout the study. Mechanistic studies investigating serologic and cellular responses to OIT and using purified peanut reagents were performed, as previously described,[13] on the subjects enrolled at one of the study sites because of the availability of specimens there. Additional details about these assays can be found in the Methods section in this article's Online Repository.

Follow-up

A 10-question telephone survey was developed to assess post-OIT dietary habits, safety, and beliefs/attitudes after study completion. Contact was attempted with all subjects who had an evaluable outcome. The questionnaire is available in the Methods section in this article's Online Repository.

Statistical methods

We computed averages, variances, frequencies, proportions, and graphic displays for all clinical and immunologic variables (GraphPad Software, La Jolla, Calif). We used Wilcoxon rank sum and Mann-Whitney tests for between-group comparisons of immunologic and facilitated antigen binding (FAB) data, respectively, at single time points. Kruskal-Wallis and Fisher exact tests were used for between-group comparisons of questionnaire data. For longitudinal analyses, we used Bonferroni-corrected, nonparametric, 2-way, repeated-measures ANOVA or simple linear regression. The area under the receiver operating curve was calculated to determine between-group predictors. P values of less than .05 were considered significant.

RESULTS

Subjects' demographics

Thirty-nine subjects were originally enrolled in the trial, and ultimately, 24 (62%) had an evaluable outcome with respect to sustained unresponsiveness (Fig 1). Six (15%) of 39 enrolled subjects withdrew for allergic side effects; the remaining 9 withdrew for personal or other reasons. Clinical and demographic