Administration of a probiotic with peanut oral immunotherapy: A randomized trial

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Background: Coadministration of a bacterial adjuvant with oral immunotherapy (OIT) has been suggested as a potential treatment for food allergy.

Objective: To evaluate a combined therapy comprising a probiotic together with peanut OIT.

Methods: We performed a double-blind, placebo-controlled randomized trial of the probiotic *Lactobacillus rhamnosus* CGMCC 1.3724 and peanut OIT (probiotic and peanut oral immunotherapy [PPOIT]) in children (1-10 years) with peanut allergy. The primary outcome was induction of sustained unresponsiveness 2 to 5 weeks after discontinuation of treatment (referred to as possible sustained unresponsiveness). Secondary outcomes were desensitization, peanut skin prick test, and specific IgE and specific IgG_4 measurements.

Results: Sixty-two children were randomized and stratified by age (≤5 and >5 years) and peanut skin test wheal size (≤10 and >10 mm); 56 reached the trial's end. Baseline demographics were similar across groups. Possible sustained unresponsiveness was achieved in 82.1% receiving PPOIT and 3.6% receiving placebo ($P < .001$). Nine children need to be treated for 7 to achieve sustained unresponsiveness (number needed to treat, 1.27; 95% CI, 1.06-1.59). Of the subjects, 89.7% receiving PPOIT and 7.1% receiving placebo were desensitized ($P < .001$). PPOIT was associated with reduced peanut skin prick test responses and peanut-specific IgE levels and increased peanut-specific IgG_4 levels (all $P < .001$). PPOIT-treated participants reported a greater number of adverse events, mostly with maintenance home dosing.

Conclusion: This is the first randomized placebo-controlled trial evaluating the novel coadministration of a probiotic and peanut OIT and assessing sustained unresponsiveness in children with peanut allergy. PPOIT was effective in inducing possible sustained unresponsiveness and immune changes that suggest modulation of the peanut-specific immune response. Further work is required to confirm sustained unresponsiveness after a longer period of secondary peanut elimination and to clarify the relative contributions of probiotics versus OIT. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Peanut allergy, oral immunotherapy, probiotic, immune-modifying adjuvant, tolerance, sustained unresponsiveness, desensitization, peanut-specific IgE, peanut-specific IgG_4*

The prevalence of food allergy has increased, particularly in westernized countries.[1-3] Food allergy is estimated to affect up to 8% of children and 2% of adults,[4,5] and a recent Australian study reported challenge-proved food allergy in 10% of 12-month-old infants, with 3% of infants having peanut allergy.[6] The need for a curative treatment is greatest for peanut allergy because this is usually lifelong and the most common cause of anaphylaxis-related fatality.[3,7,8]

Oral immunotherapy (OIT) has been explored as a strategy to induce tolerance.[9] Although studies have shown that OIT for egg, milk, or peanut can consistently induce desensitization (ie, the transient ability to tolerate a food that is lost when OIT is stopped), its ability to induce tolerance (ie, the sustained ability to tolerate a food even after OIT is stopped) remains uncertain.[9-12] Desensitization might not be an optimal outcome for some patients with food allergy because they remain allergic to their food allergen, and serious allergic reactions to maintenance OIT doses can occur despite months to years of treatment.[13,14] Although an effective treatment for food allergy would be

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Supported by the Food Allergy and Anaphylaxis Network (FAAN), the Murdoch Childrens Research Institute, Perpetual Philanthropy (grant ID 493), the CASS Foundation, the Financial Markets Foundation for Children and the National Health and Medical Research Council Australia (NHMRC project grant no. 1029690). Nestlè Health Science were provided a copy of the final draft before submission (as required by a Material Transfer Agreement).

Disclosure of potential conflict of interest: M. L. K. Tang has received research support from the National Health and Medical Research Council Australia (NHMRC grant no. 1029690), the Murdoch Children's Research Institute, Perpetual Trustees (grant ID 493), the CASS Foundation, Financial Markets Foundation for Children, and the Food Allergy and Anaphylaxis Network; is a member of the Scientific Advisory Board on Immunity and Allergy and a member of the Medical Advisory Board Australia New Zealand for Danone Nutricia; is a member of the Medical Advisory Board Oceania for Nestlè Nutrition Institute; has received speakers' fees from Danone Nutricia; and has received travel support from the IUIS Primary Immune Deficiency Expert Committee and the World Allergy Organization. W. Burks is a board member for the Food Allergy Initiative, the *Journal of Allergy and Clinical Immunology*, the Food and Drug Administration, Food Allergy Research and Education, and the American Academy of Allergy, Asthma & Immunology; serves on the grant review board for the a National Institutes of Health Study Section; has consultant arrangements with Abbott Laboratories, Dow AgroSciences, McNeill Nutritionals, Merck, Novartis Pharma AG, Schering Plough, Unilever, ExploraMed Development, Nordic Biotech Advisors, Nutricia North America, Perrigo Company, Portola Pharmaceuticals, Regeneron Pharmaceuticals, Perosphere, ActoGenIX, SRA International, Genentech, and Sanofi US Services; is employed by Duke University and the University of North Carolina–Chapel Hill; has received research support from the National Institutes of Health (grant no. 5R01-AI-068074-09) and the Wallace Research Foundation; has received payment for lectures from Mylan Specialty and Levine's Children's Hospital; has received stock in Allertein; has received personal fees from GLG Research; is a minority stockholder in Mastcell Pharmaceuticals; and was a 2012 participant in Orange Ridge Associated Universities. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication May 21, 2014; revised November 22, 2014; accepted for publication November 26, 2014.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2014.11.034

Abbreviations used
AE: Adverse event
DBPCFC: Double-blind, placebo-controlled food challenge
FDA: US Food and Drug Administration
IQR: Interquartile range
NIAID: National Institute of Allergy and Infectious Diseases
NNT: Number needed to treat
OIT: Oral immunotherapy
OR: Odds ratio
PPOIT: Probiotic and peanut oral immunotherapy
RCH: Royal Children's Hospital
RCT: Randomized controlled trial
RR: Risk ratio
SAE: Serious adverse event
sIgE: Specific IgE
$sIgG_4$: Specific IgG_4
SPT: Skin prick test

expected to induce a sustained ability to tolerate a food, few studies have assessed for this outcome after OIT, and results have been conflicting.[15-19] Moreover, it is increasingly recognized that the ability to tolerate a food after discontinuation of OIT might not be maintained; hence the term sustained unresponsiveness has been proposed in preference to tolerance when describing food allergy immunotherapy trial outcomes.[16,20]

Studies of subcutaneous and sublingual immunotherapy for allergic rhinitis using novel combinations of allergen together with bacterial adjuvants or Toll-like receptor ligands have reported enhanced tolerogenic effect.[21-26] Therefore we postulated that such a combined immunotherapy approach incorporating a probiotic bacterial adjuvant together with allergen OIT might offer an effective treatment for food allergy. Moreover, because there was no convincing evidence that allergen OIT alone was effective in promoting sustained unresponsiveness at the time our randomized controlled trial (RCT) was designed and initiated, we elected to undertake a clinical trial evaluating whether coadministration of *Lactobacillus rhamnosus* CGMCC 1.3724 (NCC4007) and peanut OIT can induce sustained unresponsiveness to peanut among children with peanut allergy (Australian New Zealand Clinical Trials Registry ACTRN 12608000594325, 25/11/2008). This probiotic was selected based on its demonstrated tolerance-promoting effects, including induction of regulatory T and T_H1 cytokine responses.[27-30]

METHODS

Study design

We performed a double-blind, placebo-controlled randomized trial combining the probiotic *Lactobacillus rhamnosus* and peanut OIT (ie, probiotic and peanut oral immunotherapy [PPOIT]) for 18 months in 62 children aged 1 to 10 years with peanut allergy (see Fig E1 in this article's Online Repository at www.jacionline.org). Additional details of the study protocol and recruitment are available in the Methods section and Table E1 in this article's Online Repository at www.jacionline.org.

Randomization and masking

Randomization was stratified by age (≤5 or >5 years) and peanut skin prick test (SPT) wheal size (≤10 or >10 mm) by using random block sizes of 2 or 4 because most children who outgrow peanut allergy do so in the first 5 years of life[31] and because smaller SPT wheal size is associated with a greater likelihood of natural resolution.[16] The study statistician generated the randomization schedule, which was provided to the Royal Children's Hospital (RCH) clinical trials pharmacist, who prepared individual treatment doses for each randomized child coded by sequential study number. Participants, outcome assessors, and statisticians were blinded to the randomized allocation.

Study conduct

The active treatment group received *Lactobacillus rhamnosus* CGMCC 1.3724 (NCC4007; provided by Nestlé Health Science, Konolfingen, Switzerland) at a fixed dose of 2×10^{10} colony-forming units (freeze-dried powder) once daily together with peanut OIT (peanut flour, 50% peanut protein; Golden Peanut Company, Alpharetta, Ga) once daily according to the peanut OIT protocol (Table I) for 18 months. The placebo group received placebo (maltodextrin) and placebo (maltodextrin, brown food coloring, and peanut essence) once daily. Active and placebo OIT products were similar in taste, color, and smell. The peanut OIT protocol (Table I) comprised a 1-day rush induction phase, a build-up phase with updosing every 2 weeks to a maintenance dose of 2 g of peanut protein (8 months), and a maintenance phase (10 months); total OIT was 18 months. Where the build-up phase was longer than 8 months (because of treatment reactions, see the footnote in Table I) but less than 12 months, the maintenance phase was adjusted to preserve a total of 18 months of OIT. For subjects taking more than 12 months to reach maintenance, the total duration of OIT was extended to ensure a minimum of 6 months of maintenance dosing.

An oral peanut double-blind, placebo-controlled food challenge (DBPCFC; cumulative dose, 4 g of peanut protein) was performed on the last day of study treatment (T1) to assess for desensitization. Children who passed the T1 DBPCFC underwent a second DBPCFC performed after an interval of 2 or more weeks off study treatment (T2), during which time they continued a peanut elimination diet, to assess for sustained unresponsiveness. This interval of secondary peanut elimination was selected based on the published recommendation by the National Institute of Allergy and Infectious Diseases (NIAID)–US Food and Drug Administration (FDA) Workshop on Food Allergy Clinical Trial Design[32]; however, it is acknowledged that a longer period of at least 4 weeks would now be advisable. DBPCFC failure occurred if objective symptoms were noted during the challenge procedure.[33] Subjects who failed the T1 DBPCFC were classified as allergic; those who passed the T1 DBPCFC were classified as desensitized. Subjects who passed both the T1 and T2 DBPCFCs were classified as having attained sustained unresponsiveness. Subjects returned for clinical interviews (including questionnaire) and SPTs at 3 months after treatment (T3). Additional details of study conduct are available in the Methods section in this article's Online Repository.

Data collection

SPTs to peanut and other common food and inhalant allergens were performed, and blood samples were collected at baseline (T0), completion of PPOIT treatment (T1), and 3 months after treatment (T3). Serum peanut-specific IgE (sIgE) and peanut-specific IgG_4 ($sIgG_4$) levels were measured by using the ImmunoCAP 250 (provided in part by Phadia AB, Uppsala, Sweden).

Severe adverse events (AEs) were defined as any symptom that prevents daily activities and might require therapeutic intervention. A serious adverse event (SAE) was defined according to standard criteria (see the Methods section in this article's Online Repository). An independent safety and data monitoring committee maintained trial observation. Parents of participating children provided written consent. The RCH Human Research and Ethics Committee provided ethics approval. The trial was registered with the Australian New Zealand Clinical Trials Registry before commencement (ACTRN 12608000594325, 25/11/2008).

Outcome measures

The primary outcome was sustained unresponsiveness (passed the T1 and T2 DBPCFCs). The term tolerance was assigned for the primary outcome in