Probiotic and peanut oral immunotherapy: a breakthrough for allergy treatment

Peanut allergy, which affects 1–5% of children, is a potentially lifelong problem associated with unpredictable and severe reactions.[1,2] Treatments to mitigate reaction severity, desensitise patients to withstand inadvertent peanut ingestion, and—ideally—cure the allergy outright are urgently needed.[1] Oral immunotherapy, in which allergic patients are orally re-fed titrated amounts of an allergen in a highly supervised setting overseen by experienced health-care providers, is a promising strategy in development.[3] The goal is to achieve either desensitisation (a temporary state of tolerance to a specified allergen quantity, requiring re-exposure to this dose every 24–36 h) or sustained unresponsiveness, a tolerised state in which patients can eat the allergen ad libitum without re-exposure.

Although data show that oral immunotherapy can safely desensitise most children, only a very small proportion ever develops sustained unresponsiveness.[3] Furthermore, there is a paucity of data for long-term outcomes of oral immunotherapy and poor understanding of caregiver expectations or goals of therapy.[3-5] Caregiver treatment preferences were assessed in only one study,[6] which showed that they preferred lower target doses of oral immunotherapy with the aim of achieving protection against small accidental exposures, rather than higher doses targeting sustained unresponsiveness but risking more adverse events during the titration phase. This strategy for peanut oral immunotherapy has been adopted by the pharmaceutical industry, and a low-dose product is being tested in a phase 3 trial (NCT02635776). Substantial gains in peanut oral immunotherapy research have otherwise plateaued in the past few years.[3]

However, in *The Lancet Child & Adolescent Health*, Kuang-Chih Hsiao and colleagues[7] report a breakthrough that has the potential to reinvigorate enthusiasm in peanut oral immunotherapy research. They detail the 4-year follow-up of participants who completed a randomised, placebo-controlled trial of an innovative coadministration of the probiotic *Lactobacillus rhamnossus* CGMCC with peanut oral immunotherapy (2 g peanut protein). The probiotic is postulated to help to reduce adverse events related to oral immunotherapy and enhance the body's ability to develop tolerance. In 2015, this same group reported the initial results[8] of the trial: 26 (89%) of 29 participants in the combined probiotic and peanut oral immunotherapy (PPOIT) group achieved desensitisation after 1 year of therapy, compared with two (7%) of 28 participants in the placebo group. 23 (82%) of 28 PPOIT-treated participants attained sustained unresponsiveness upon food challenge 2 weeks after discontinuation of PPOIT.[8]

In this study, 48 (86%) of the 56 original participants were followed up for 4 years after treatment cessation. 16 (67%) of 24 participants in the PPOIT group were still eating peanuts ad libitum after 4 years, compared with one (4%) of 24 participants from the placebo group (number needed to treat 1·6 [95% CI 1·2–2·4]), suggesting long-term efficacy. As an additional test of long-term efficacy, 27 participants agreed to discontinue any peanut consumption for 8 weeks and undergo double-blind placebo-controlled peanut challenge. Seven (58%) of 12 PPOIT-treated participants attained sustained unresponsiveness, compared with one (7%) of 15 placebo-treated participants (number needed to treat 1·9 [95% CI 1·2–4·8]). This study is the first demonstration of such prolonged sustained unresponsiveness with any form of peanut oral immunotherapy, and the best data so far showing long-term efficacy of oral immunotherapy for any food allergen.

The therapeutic effect shown is remarkable and redefines the notion of sustained unresponsiveness. The broader context of what these findings potentially represent is a demonstration of true tolerance, whereby patients could mimic the eating habits of non-allergic individuals. During the 4 years after the parent trial ended, more than half the participants in the PPOIT group were eating 2 g or more of peanut as infrequently as once or twice per week, and 16 (80%) of the 20 who initially achieved 2-week sustained unresponsiveness were regularly eating peanuts. This finding in itself is novel: in no other study of oral immunotherapy have individuals been able to ingest the allergen with this infrequency and remain non-reactive.[3] However, the true breakthrough is that, after 4 years of such infrequent consumption, seven of the PPOIT-treated participants who stopped any peanut ingestion for 8 weeks and then underwent

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double-blind placebo-controlled food challenge—which would select out anyone who was merely desensitised with a liberal re-exposure interval—attained sustained unresponsiveness. Thus, these seven PPOIT-treated patients showed true, probably lasting tolerance, meaning that they can eat peanut whenever they chose, even very infrequently, similar to a non-allergic person. For researchers, the allergic child, and their caregivers, this finding is the most meaningful change possible.

Assuming that these results can be replicated in a larger trial, caregiver preferences might shift back towards higher oral immunotherapy doses, which now might seem more worth the risk. Furthermore, additional data are needed about the precise effect of the probiotic. In their initial hypothesis, the authors stated that the probiotic could add to tolerance via effects on short-chain fatty acids and regulatory T cells; no data are available for continued probiotic intake during the follow-up period, although participants were unlikely to have consumed the probiotic dose in PPOIT (equivalent to 20 tubs of yogurt per day).[8,9] Results from a study[10] based on the 2015 published outcomes showed that PPOIT is probably cost effective compared with allergen avoidance, which suggests further benefits and potential. However, additional research is essential to understand caregiver preferences, better align therapeutic goals, and refine cost-effectiveness models.

Despite achieving an important milestone, this study included small patient numbers, did not retain all participants in long-term follow-up , and did not include entry peanut challenge to show participants' baseline threshold (which was not standard practice in early oral immunotherapy studies, but is routinely done now) or comparison of oral immunotherapy with PPOIT to delineate the effect that is attributable to the probiotic. These limitations are being addressed in a multicentre trial aiming to replicate these findings. The field of allergy and immunology anxiously awaits these results. Successful replication of these data could lead to broader questions of generalisability of the probiotic plus oral immunotherapy approach to other allergens and possible abandonment of oral immunotherapy without probiotic coadministration.

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