

STOPping peanut allergy: the saga of food oral immunotherapy



Food allergy affects roughly 15 million Americans and 17 million Europeans, most being young children.^{1,2} At present, there is no known treatment or cure. However, oral immunotherapy (OIT) is a promising investigational therapy which aims to produce allergen desensitisation through graduated dose exposure to an allergen (eg, temporary tolerance from continuing controlled exposure to an allergen, which wanes if ongoing exposure is withdrawn). Over time, a lasting tolerance to incidental allergen ingestion might remove the need for continued ongoing exposure.³

In *The Lancet*, Katherine Anagnostou and colleagues report the results of the STOP II trial,⁴ a two-step, phase 2, unmasked, randomised controlled crossover trial of peanut OIT in 99 children aged 7–16 years, inclusive of all severities of peanut allergy. In the first phase, participants were randomly assigned to receive either 26 weeks of OIT to 800 mg of peanut protein, or peanut avoidance (the standard of care). Both groups then underwent a double-blind, placebo-controlled, peanut challenge, and in a second phase the control group was offered the 26 week OIT protocol and challenge. Among OIT participants, 91% (95% CI 79–98) were desensitised to 800 mg, the equivalent of five peanuts. In terms of the trial's primary outcome, 24 of 39 OIT participants were desensitised to 1400 mg of peanut protein (the peak dose offered in the trial), as compared with none of 46 participants in the control group (risk difference 62%, 95% CI 43–77). Compared with control participants, those completing OIT had a significant 25-fold increase of their no observed adverse effect level over baseline, and their caregivers had a significant improvement in quality of life. Adverse effects were mild. Only two OIT doses induced symptoms needing epinephrine (both in the same patient, who withdrew), although 20% of all OIT participants reported adverse events.

Previous studies have concluded that OIT can safely produce desensitisation to peanut and other allergens among selected, but not all, participants. These studies have significant methodological concerns, including small sample sizes, selection bias (involving referral centre populations of older children without past severe reactions and with motivated caregivers), and lack of control groups or pre-OIT challenge to confirm that the patient still has persistent allergy.^{5–10} In particular,

caregiver participation bias might substantially affect study results, although this is probably an unavoidable constraint dictated by limited selection pools. In past peanut OIT studies, high proportions of participants developed adverse reactions, including anaphylaxis; dropout was high; and no mechanism of action for the immunological effects was clearly identified. Moreover, because adverse events have been reported at the dose level (the convention for inhalant/venom immunotherapy) and not the patient level, the high total proportion of all participants experiencing adverse reactions has been obscured when spread across several thousand total doses. Notably, patients deliberately screened to be less reactive by history have experienced more severe reactions than baseline during OIT, and not all participants achieve desensitisation.^{6,7,9,11} Poor data exist to predict successes from failures. Therefore, previous conclusions that OIT is safe and effective might be somewhat subjective.

Anagnostou and colleagues have avoided most of these methodological concerns. They report fewer side-effects with little epinephrine use among OIT participants, enrolled community participants and individuals with previous severe peanut reactions, required entry food challenges, and focused on quality of life as a key outcome.⁴ These are substantial changes from earlier peanut OIT studies, but a few problems with the methods remain, such as lack of masking, participation bias (use of a community sample recruited through a food allergy advocacy group), a roughly 10% dropout, unclear power for the analysis of the quality of life outcome, and use of a truncated peak dose (1400 mg) with uncertain clinical importance compared with other trials that far exceeded this peak dose.^{4,5,8–10,12}

Therefore, the validity and generalisability of past and ongoing OIT studies should be questioned, as with any early phase research. Although these concerns should not diminish the value of the results so far, which are exceptionally promising, OIT remains experimental.¹³ OIT is not ready for clinical use until the short-term effects have been comprehensively proven, and the long-term side-effects, mechanism of action, and outcomes are known. Furthermore, a common protocol and delivery vehicle should be decided upon, since this has varied across studies.^{4,6,8–10,12} It is unknown if OIT can



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produce lasting tolerance, a key outcome. Although one peanut study and one egg study have shown that certain participants can withstand a 2 week (peanut) or 4–6 week (egg) interruption of OIT and remain tolerant, these advances are balanced by reports from other OIT studies (milk) of participants developing eosinophilic oesophagitis or redeveloping the allergy after months to years of tolerating therapy.^{9,11,14,15} Both are unwanted outcomes, and highlight issues still to be clarified.

Continued OIT studies are needed, but with larger samples that include severely reactive individuals, very young patients, and individuals from both the community and referral centre settings to encompass a robust food-allergic population. Future studies must establish if OIT is cost-effective, as well as continue to explore how OIT affects quality of life. Importantly, caregiver goals (eg, achieving a cure vs increasing the reaction threshold) need to be understood, which might need different protocols to be developed if many goals exist. Understanding the range and degree of effect is also paramount. There is poor understanding of the degree of heterogeneity in disease phenotype that exists across the food-allergic population. However, if there is also heterogeneity of treatment effect for OIT then this must be comprehensively shown so the correct populations of food-allergic individuals receive the therapy. It would be naive to view OIT as a one size fits all treatment for food allergy but, on the contrary, it would be short-sighted to deem OIT a failure if only a small subset of food-allergic individuals benefit.

In conclusion, although Anagnostou and colleagues provide further evidence that OIT is a potential treatment for food allergy,⁴ more high-quality data are needed. It is important to understand that OIT research cannot be rushed, and is years away from routine clinical use. Investigative groups need time to refine protocols, revalidate data, understand the mechanisms of OIT, and minimise adverse effects. This must be done without

added pressure or heightened expectations to quickly produce a marketable therapy.

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