

Peanut oral immunotherapy: balancing benefits and risks for individuals



Peanut allergy affects around 2% of the population.¹ Fatal anaphylactic reactions are rare but can occur.² It has a considerable negative impact on the quality of life of patients and their families,³ and all patients need to avoid peanuts and carry self-injectable adrenaline. With many foods being labelled as “may contain nuts”, complete avoidance is a challenge.⁴ Until this decade, no treatment for food allergy was available;^{5,6} hence considerable efforts were made to develop oral immunotherapy for food allergy.⁷

The systematic review and meta-analysis by Derek Chu and colleagues in *The Lancet* summarises the evidence for oral immunotherapy for peanut allergy.⁸ Traditionally, the primary outcome for food allergy oral immunotherapy trials is passing a graded oral food challenge because this is an objective outcome that can be carefully controlled. In contrast, for their primary outcome, Chu and colleagues have used the more patient-centred endpoint of peanut-induced anaphylaxis, either as a result of unplanned exposure to peanuts or as a result of the daily doses of peanuts in the oral immunotherapy. This endpoint arguably provides a much better summary of a patient's experience in day-to-day living than one oral peanut challenge.

Their systematic review⁸ included 1041 participants (median age 8.7 years [IQR 5.9–11.2]; 39% female participants) across 12 randomised controlled trials of peanut oral immunotherapy. Participants in the oral immunotherapy groups in these trials were given increasing doses of peanuts on a daily basis until they reached a maintenance dose. The median starting dose of peanut protein was 0.5 mg and the median maintenance dose was 2000 mg (about four peanuts). The meta-analysis found that oral immunotherapy actually increased the risk of anaphylaxis (relative risk 3.12 [95% CI 1.76–5.55]; no important heterogeneity).⁸ This outcome contrasts with passing an oral peanut challenge, which was much more probable with oral immunotherapy (12.4 [6.82–22.61]). Oral immunotherapy also did not improve quality of life in the small number of studies that assessed it (1.21 [0.87–1.69]).

The key criticism of this systematic review⁸ is inherent in its method because studies with different

designs were grouped together. Although most of the trials compared immunotherapy with placebo, avoidance was the comparator in three studies and sublingual immunotherapy in one study. This might have been expected to add some heterogeneity to the results. However, there was minimal heterogeneity and no difference between the different designs in their preplanned sensitivity analyses. This lack of heterogeneity is even more surprising because of the different preparations of peanut products used and the more than ten-times difference in maintenance doses. Interestingly, the maintenance dose was not associated with the risk of anaphylaxis during follow-up in the trial. In addition, the systematic review focused on desensitisation and did not account for whether the therapy continued to be effective after it had been discontinued (ie, development of tolerance).

The authors estimated that peanut oral immunotherapy was associated with 151 (95% CI 54–323) more episodes of anaphylaxis per 1000 patients.⁸ They used a figure of 71 episodes of anaphylaxis per 1000 as the baseline risk on the basis of historical data. Such an approach overlooks the differing patterns of these events. Participants in the oral immunotherapy groups would have had anaphylaxis in association with daily doses of peanuts at home, where they would have felt more in control. Participants in the comparator groups would have had anaphylaxis mainly when they were away from home, where they would have felt less in control. Immunotherapy has always needed a consideration of the balance between efficacy and safety. Particularly, anxious patients with frequent reactions might benefit from exchanging reactions away from home for reactions at home.

Unfortunately, the trials have not provided information about which participants benefited most from the intervention. Only a few trials collected quality-of-life data and none reported cost-effectiveness data. These data are essential. A mixed-methods approach would be helpful to provide insights into the balance between the emotions of living with a severe allergy and with oral immunotherapy.

Undoubtedly oral immunotherapy reduces the likelihood of reacting to peanuts in a controlled clinic



Tim Grist Photography/Getty Images

Published Online
April 25, 2019
[http://dx.doi.org/10.1016/S0140-6736\(19\)30767-6](http://dx.doi.org/10.1016/S0140-6736(19)30767-6)
See Online/Articles
[http://dx.doi.org/10.1016/S0140-6736\(19\)30420-9](http://dx.doi.org/10.1016/S0140-6736(19)30420-9)

setting, its overall side-effect profile means that patients seem to have more allergic reactions while on therapy. Trading treatment-related side-effects at home for allergic reactions to accidental exposures out of the house (ie, in social situations) might be beneficial for some patients. However, it is not clear which patients might benefit most and what the relative balance of reactions in and out of patients' homes would be. It would also be useful to compare oral with epicutaneous immunotherapy. Although epicutaneous immunotherapy is less effective, it has a better safety profile than oral immunotherapy, which some patients might find more acceptable.⁹ Finally, we should not forget that we now know that the early introduction of peanut products into the infant diet can prevent most cases of peanut allergy.¹⁰ Moving forward we need to develop implementation strategies to reduce the number of patients with peanut allergy.

**Graham Roberts, Elizabeth Angier*

Clinical and Experimental Sciences and Human Development and Health, Faculty of Medicine (GR), and Primary Care and Population Sciences (EA), University of Southampton, Southampton, UK; NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton SO16 6YD, UK (GR); and The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK (GR) g.c.roberts@soton.ac.uk

GR and EA are members of the European Academy of Allergy and Clinical Immunology Allergen Immunotherapy Guidelines Group, which has recently published guidelines on immunotherapy.

- 1 Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A, on behalf of the EAACI Food Allergy and Anaphylaxis Guidelines Group. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. *Allergy* 2014; **69**: 992–1007
- 2 Turner PJ, Gowland MH, Sharma V, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992–2012. *J Allergy Clin Immunol* 2015; **135**: 956–63.
- 3 Stensgaard A, Bindslev-Jensen C, Nielsen D, Munch M, DunnGalvin A. Quality of life in childhood, adolescence and adult food allergy: patient and parent perspectives. *Clin Exp Allergy* 2017; **47**: 530–39.
- 4 DunnGalvin A, Chan CH, Crevel R, et al. Precautionary allergen labelling: perspectives from key stakeholder groups. *Allergy* 2015; **70**: 1039–51.
- 5 Muraro A, Werfel T, Hoffmann-Sommergruber K, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. *Allergy* 2014; **69**: 1008–25.
- 6 Stiefel G, Anagnostou K, Boyle RJ, et al. BSACI guideline for the diagnosis and management of peanut and tree nut allergy. *Clin Exp Allergy* 2017; **47**: 719–39.
- 7 Pajno GB, Fernandez-Rivas M, Arasi S, et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy. *Allergy* 2018; **73**: 799–815.
- 8 Chu DK, Wood RA, French S, et al. Oral immunotherapy for peanut allergy: a systematic review and meta-analysis of efficacy and safety. *Lancet* 2019; published online April 25. [http://dx.doi.org/10.1016/S0140-6736\(19\)30420-9](http://dx.doi.org/10.1016/S0140-6736(19)30420-9).
- 9 Fleischer DM, Greenhawt M, Sussman G, et al. Effect of epicutaneous immunotherapy vs placebo on reaction to peanut protein ingestion among children with peanut allergy: the PEPITES randomized clinical trial. *JAMA* 2019; published online Feb 22. DOI:10.1001/jama.2019.1113.
- 10 Du Toit G, Roberts G, Sayre PH, et al. Randomized trial of peanut consumption in infants at risk for peanut allergy. *N Engl J Med* 2015; **372**: 803–13.