

described it during home dosing, in diaries or interview. It was therefore not known whether this represented bronchospasm or another less severe respiratory condition, when the patient self-treated at home. Nonetheless, these reactions were all classified as 'wheeze'. The low rate of intramuscular epinephrine use at home, and improvement after only minimal medication use, implies that very few of the reported wheeze episodes represented significant bronchospasm, reinforcing our assertion of a good safety profile.

Overall assessment

The authors identify three areas that they claim represent a 'great unknown'.

The impact of extrinsic factors is no longer a 'great unknown'. Many are recognized from everyday clinical practice as factors that make reactions worse, for example exercise or illness. Much has also been learned about this subject from the early studies of food OIT,²⁻⁴ and several factors are clearly defined. Patients in food OIT trials are now proactively warned about these, and this advice can be translated into standard clinical care to accompany OIT.

It is clear that treatment can achieve a state of protective desensitization in the majority of study participants. A small number may be able to stop treatment in the shorter term and maintain tolerance, but for the rest a reliance on continuing desensitization still represents a positive outcome. A significant improvement in quality of life clearly indicates this is acceptable.

A tiny number of cases of suspected eosinophilic disease have been reported during OIT.^{5,6} This is a histological diagnosis, and no study has provided a tissue diagnosis, let alone confirmed an association. Rare conditions, if they occur more frequently during OIT, will be identified after treatment of large numbers of patients in postmarketing studies.

Finally, the authors did not comment on the imperative for providing novel preventative treatments for peanut allergy. Peanut allergy affects one in 50 schoolchildren in the U.K. and has a significant effect on the quality of life of those affected, due mainly to the fear of severe, life-threatening reactions and death. Avoidance has been the mainstream of management up until now, but there is a clear need for a disease-modifying treatment that will have the potential to minimize the risk of accidental reactions and improve quality of life.

Funding sources

None.

Conflicts of interest

None declared.

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More work needed to crack the nut

DOI: 10.1111/bjd.14159

Summary

The STOP II study provides high-quality evidence on the efficacy, safety and impact on quality of life of oral immunotherapy (OIT) in peanut-allergic children. Although the results are promising, significant concerns and knowledge gaps remain regarding the safety of OIT, its ability to induce long-term tolerance once regular peanut intake is stopped and, accordingly, long-term adherence. Peanut OIT therefore needs to be restricted to research studies aiming to complete the current evidence gaps.

As the largest randomized controlled trial on the subject to date, the STOP II study provides high-quality evidence on the efficacy, safety and impact on quality of life of oral immunotherapy (OIT) in peanut-allergic children.¹ Uniquely, STOP II is the first published study so far on peanut OIT that was adequately powered at study outset. On intention-to-treat analysis, two-thirds (33 of 49) of patients initially included in the active group were able to eat the target dose of 800 mg peanut protein (about five peanuts) without reacting after 6 months – a treatment effect that is likely to

provide protection against accidental reactions in the community.

However, significant concerns and knowledge gaps remain regarding the safety of OIT, its ability to induce long-term tolerance once regular peanut intake is stopped and, accordingly, long-term adherence. Peanut OIT therefore needs to be restricted to research studies aiming to complete the current evidence gaps.

Some safety data arising from the STOP II study are worrying, although no serious adverse reactions occurred. Most patients – at least 81% – experienced allergic reactions, and 22% had lower-respiratory-tract symptoms ('wheeze') at some stage, which should be regarded as potentially severe. That these reactions were not treated with intramuscular adrenaline is in conflict with current management guidelines for food-induced reactions in the community. This raises concerns about the implementation of OIT and its safety in a wider population if, as suggested by the authors, caregivers seem to be reluctant to use adrenaline autoinjectors when indicated. The lack of safety data beyond 6 months also hampers the ability to draw conclusions in this regard.

The absence of data on long-term tolerance induction (after stopping daily peanut dosing) and adherence needs to be addressed. Unfortunately, existing evidence is not encouraging. An uncontrolled study reported that 50% of patients (12 of 24) successfully desensitized to peanut lost this effect 4 weeks after stopping OIT.² In a study of OIT for cow's-milk allergy, only one-third of treated children were able to tolerate a regular serving of milk 1–5 years after starting OIT,³ despite milk being a regular component of our diets, in contrast to peanut. Long-term adherence to regular peanut doses may be difficult. It is unclear as to how peanut OIT safety might be compromised beyond initial up dosing by suboptimal adherence, and how both safety and adherence are affected by (co)-factors such as asthma exacerbations, exercise or viral infections, which can contribute to unexpected symptoms. Near-fatal reactions have been reported in poorly compliant teenagers undergoing OIT to cow's milk and egg in these circumstances.⁴

The STOP II study showed that more 'successful' OIT (i.e. increased threshold of reactivity to peanut) was associated with less severe prior reactions, higher initial threshold, younger age and lower peanut-specific IgE levels. This suggests that peanut OIT is less successful in children at higher risk for persistent and/or more severe peanut allergy – the very patients who have most to benefit from OIT – and is consistent with OIT studies on cow's milk and egg.^{5,6}

Finally, OIT involves intense commitment and resources from caregivers and patients, as well as healthcare professionals, both during induction and in the long-term. Whether this can be implemented outside the research setting is debatable. So far, no cost-effectiveness studies have been performed. Likewise, the impact of OIT on quality of life in the longer term – especially as reported by the children/teenagers themselves – has not been evaluated.

In conclusion, although the STOP II study data are promising, more research is needed to improve safety and provide better evidence on the long-term effectiveness of peanut OIT, before it can be implemented in routine clinical practice.

Funding sources

None.

Conflicts of interest

None declared.

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