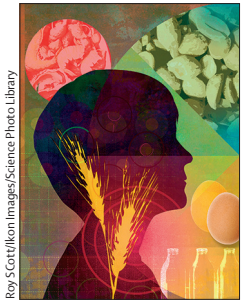


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Sustained unresponsiveness in peanut oral immunotherapy



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Peanut allergy is a potentially life-threatening disease with substantial impact on the quality of life of patients and carers.¹ Many initiatives are underway to develop treatment alternatives for strict peanut avoidance. Subcutaneous immunotherapy with aqueous peanut extract was found to be too dangerous.² Alternatives such as sublingual, epicutaneous, and oral immunotherapies are being tested. So far, oral immunotherapy (OIT) has proved most effective in achieving meaningful desensitisation while on therapy. In a few smaller peanut OIT trials, sustained unresponsiveness around 1 month after treatment cessation was found to be variably disappointing.³

To evaluate sustained unresponsiveness for up to 1 year, Sharon Chinthrajah and colleagues⁴ report in *The Lancet* their large randomised, double-blind, placebo-controlled phase 2 OIT trial in 120 patients with peanut allergy (aged 7–55 years; 68% of whom were male). Patients were treated for 2 years with high-dose peanut protein (4000 mg; n=95 [79%]) or placebo (n=25 [21%]). In year 3, high-dose treatment was replaced by either placebo (peanut-0 group, n=60 [50%]) or low-dose treatment (peanut-300 group, n=35 [29%]). At the end of year 2, and every 3 months during year 3, patients were given a double-blind, placebo-controlled food challenge. After 2 years of treatment, 80 (84%) of 95 participants passed a 4000 mg challenge (approximately equivalent to 13–16 peanuts), compared with one (4%) of 25 participants in the placebo group. Sustained unresponsiveness in year 3, under influence of cessation or low-dose treatment, was observed in 21 (35%) of 60 participants in the peanut-0 group and 19 (54%) of 35 participants in the peanut-300 group after 13 weeks, gradually declining to eight (13%) of 60 participants in the

peanut-0 group and 13 (37%) of 35 participants in the peanut-300 group after 1 year. The percentage of sustained unresponsiveness appeared to plateau in the second half of year 3, suggesting that for some patients sustained unresponsiveness might be (more) persistent. During high-dose treatment, a very high percentage of patients had mild to moderate adverse events, mainly gastrointestinal and skin related, decreasing from 89 (94%) of 95 participants in the first year to 60 (70%) of 86 participants in the second year. This decrease was paralleled by a decrease from 18 (19%) of 95 participants to 12 (13%) of 95 participants requiring epinephrine. In real-life settings, risk factors such as exercise, viral infections, or poor treatment adherence might be less consciously monitored and thereby increase the risk of severe adverse events. Continued low-dose treatment did rescue some sustained unresponsiveness and led to a clear reduction of adverse events (six [20%] of 30 participants). Analogous to immunotherapy for respiratory allergies,⁵ it is possible that 3–5 years of high-dose treatment will further increase the number of patients reaching sustained unresponsiveness, but this remains to be tested. The overall picture emerging from this study is consistent with a recent meta-analysis by Chu and colleagues.⁶ Peanut OIT can effectively desensitise, but at the cost of a high number of adverse events, and with sustained unresponsiveness being the exception rather than the rule.

The aim of peanut OIT is not to allow patients to introduce peanut into their diet. Many people have an aversion to peanuts and consequently problems adhering to high-dose OIT.⁷ Patients with the highest risk of encountering life-threatening reactions on accidental exposure to peanut are most in need of an effective treatment. Their quality of life is most

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affected. In all OIT studies so far, including this one,⁴ patients with severe anaphylaxis have been excluded for obvious reasons. Would OIT work in these patients? Adverse events will probably reach unacceptable levels, but even if sufficiently safe administration could be achieved, this study does not give too much reason for optimism. The number of adverse events and the failure to achieve (persistent) sustained unresponsiveness were both positively associated with baseline specific IgE against peanut, in particular against its major allergen Ara h 2, with baseline basophil sensitivity and low peanut-specific IgG4:IgE antibody ratios. In other words, the more a patient is sensitised without sufficient protective IgG4, the bigger the risk of adverse events and the smaller the chance for treatment success. These immunological biomarkers have also been implicated as risk factors for severe symptoms.^{8,9} The outcome of this study therefore implies that the appropriate target group for safe and effective OIT is likely to be the mildly to moderately sensitised patient, not the severely anaphylactic patient.

For patients in most urgent need of treatment—ie, those that are severely anaphylactic (highly sensitised)—hypoallergenic (safer) but more immunogenic (higher IgG4) approaches need to be explored. In respiratory allergy, subcutaneous immunotherapy has been shown to be very effective and a more potent inducer of protective IgG4.¹⁰ The availability of hypoallergenic recombinants¹¹ or chemically modified extracts¹² now offers the opportunity to explore whether subcutaneous immunotherapy might be a safe and effective alternative for the severely anaphylactic patient.

Overall, the study by Chinthrajah and colleagues⁴ has confirmed earlier reports that OIT is very effective, but the protection is rapidly lost on cessation of treatment. Because of the high number of severe adverse events,

current OIT is not a viable option for treatment where most needed—ie, in individuals with severe anaphylaxis.

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Protecting children's rights: why governments must be bold to tackle childhood obesity

The UK Chief Medical Officer's independent review of childhood obesity, *Time to Solve Childhood Obesity*, was published on Oct 10, 2019.¹ In England the prevalence of childhood obesity is too high; about 20% of children aged 10–11 years are obese (≥ 95 th centile on the UK90

growth charts).² There is widespread public support for action with three "chapters" of an ambitious plan outlined by the UK Government.^{1,3–5} Now we need a focus on implementing solutions, and the independent review calls for bold action to improve children's health.



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