

Palforzia for peanut allergy: Panacea or predicament

Over a century ago, Alfred Schofield reported in the *Lancet* treating a 13-year-old boy with an egg allergy by introducing tiny amounts of egg into his diet and incrementing the dose.¹ Commencing in December 1906 with pills containing 1/10000th part of a raw egg daily this dose was maintained for a month, before in the following month, the dose was incremented every four days until 1/1000th of a raw egg was consumed daily. Incrementing doses of pills containing raw or cooked egg alternately ensued the following month increasing to 1/500th of an egg daily. By March, he was consuming 1/250th egg, April 1/150th and June 1/33rd. In July, the pills were dropped, and he was switched to actual egg and by the end of July was consuming 1/6th of an egg daily. The amount was then rapidly increased until he ate one egg a day. The whole process had lasted 9 months, and pills had been substituted for real food towards the end of the regimen.

So many aspects of Schofield's case report are pertinent to contemporary food immunotherapy. The Cambridge group in their seminal trial of peanut immunotherapy with defatted peanut flour used a daily regimen, with nine fortnightly increments, starting at 2 mg through to a maintenance dose of 800 mg and lasting 6 months.² Ongoing daily consumption of 800 mg of peanut protein was recommended, but the vehicle was not stated. In contrast, in their earlier pilot study, at the final updose it was stated that subjects were given the choice of continuing to take peanut flour or five to seven peanuts daily (~800 mg protein).³

Aimmune have replicated what Schofield did, namely placing a food product, defatted peanut flour, into capsules or sachets (as opposed to pills) and the result is Palforzia, the first licensed product for peanut immunotherapy in the UK which has just been approved by NICE. The immunotherapy regimen with Palforzia requires an initial dose escalation day then 11 fortnightly up dosing visits. Hence, 12 allergy day case visits per child. The median number of challenges undertaken per week in UK paediatric allergy services is two. The NHS is expected to offer Palforzia to 600 children in the first year, rising to 2000 each year after that. 2000 children requires 24,000 day case visits. The entire UK food challenge capacity in the 139 units that provide food challenges is 30,076 per year. So 80% of all challenges would have to cease and be switched to day case visits for Palforzia. In the PALISADE trial, 33% of the administrations of adrenaline autoinjectors (AAI) in the Palforzia arm took place in clinic.⁴ Hence it is essential that Palforzia up dosing visits take place in an environment appropriate for the management of anaphylaxis and administration of AAI and that pressure is resisted that for logistical purposes up dosing takes place in, for example, the outpatient department.

Schofield achieved a 100% success rate for his egg tolerance induction regimen in a trial of $n = 1$. Using defatted peanut flour achieved tolerance of a daily 800 mg dose of peanut protein in 88% and to a cumulative dose of 1400 mg peanut protein in 58% (Cambridge)² and of a single dose of 600 mg (cumulative dose of ≥ 1043 mg) of peanut protein in 67% and of a single dose of 1000 mg (cumulative dose of ≥ 2043 mg) of peanut protein in 50% (Palforzia).⁴ Schofield's child completed his course of immunotherapy, whereas 21% of the children commencing Palforzia in the PALISADE trial did not complete their immunotherapy regimen.⁴

Schofield reported that having successfully completed his egg immunotherapy the 'difference to the boy is, of course, enormous'. Objectively measuring the improvement in quality of life from peanut immunotherapy has provided more variable results. Chu et al reported no change in quality of life in their systematic review of peanut immunotherapy.⁵ Reports of the improvement in quality of life for those receiving immunotherapy demonstrate selection bias through being restricted to those who successfully complete the immunotherapy, omitting the views of those who drop out during treatment. There is a real concern that for the one in five children who fail to complete a course of peanut immunotherapy there could potentially be a very negative effect on the child and family's quality of life, with them perceiving that the opportunity to improve life for the family having been lost.

The ARTEMIS trial, using Palforzia, assessed participant reported quality of life with the FAQLQ (four components) and FAIM (six components), stratified by two age bands (8–12 and 13–17).⁶ No statistically significant improvement was seen in any component for 13–17-year-olds. Improvements that exceeded the minimum clinically important difference (≥ 0.5) were seen in all four FAQLQ components in the 8–12-year-olds. However, one of these was not statistically significant. Given 20 outcomes were being assessed, adjustment should have been made for multiple comparisons which would have rendered none of the comparisons statistically significant.

Schofield's case was 13 years old. Palforzia has been approved for children age 4–17 years, with it being found to be ineffective in adults in the PALISADE trial.⁴ It is conceivable that Palforzia may be more efficacious in younger children; however, commencing peanut immunotherapy in children under 10 is confounded by the fact that up to 20% of peanut-allergic children outgrow their peanut allergy by 10 years of age spontaneously. In contrast to those undergoing peanut immunotherapy, spontaneously outgrowing peanut allergy results in life-long tolerance and, most importantly, is not dependent on ongoing regular consumption of peanut. Hence, starting

younger children with Palforzia carries the risk of including some children who would have spontaneously outgrown their peanut allergy anyway.

Schofield wrote that "some may think a great deal of trouble was taken to cure this idiosyncrasy", but immunotherapy is not a cure for most people with food allergy. After 134 weeks peanut immunotherapy followed by 26 weeks of avoidance, Jones et al found that just 21% (20/96) remained tolerant.⁷

Schofield's case appeared to experience no adverse symptoms from his regimen, but this was clearly an aberration as the process of repeatedly giving a food to which a child is allergic inevitably induces symptoms. Chu et al reported that peanut oral immunotherapy regimens considerably increase allergic and anaphylactic reactions over avoidance or placebo.⁵ Safety remains the prevailing concern with food immunotherapy, and the first fatality has been reported. In the PALISADE trial, 14% required an adrenaline autoinjector to be administered during their Palforzia immunotherapy, with an AAI being administered three times on one single occasion for one participant.⁴ This was the experience within the highly selected environment of a research randomized controlled trial. Once Palforzia is used more widely in the real world it seems likely that more untoward events will occur. Vazquez-Ortiz et al recorded three cases of life-threatening anaphylaxis during immunotherapy in Spain. In one, a 14-year-old boy missed 3 days of his maintenance OIT. Taking a dose the next day, he experienced anaphylaxis requiring three administrations of an AAI, volume expansion, inotropes, intravenous salbutamol, steroids and invasive ventilation for 48 hours.⁸

The Cambridge group's six month peanut flour regimen consisted of 18 weeks for up dosing and 8 weeks of maintenance. This achieved essentially the same efficacy as the PALISADE peanut flour protocol of 22 weeks of up dosing and 24 weeks of maintenance therapy (almost 11 months). Notably, the Palforzia prescribing information states that efficacy has been shown after at least 3 months of maintenance immunotherapy (based on the ARTEMIS trial) but does not state how long maintenance should continue for, nor when to consider switching from Palforzia to actual peanut. The Palforzia maintenance dose of 300 mg of peanut protein represents 2 UK-sized peanuts. The original Cambridge studies were content to allow their participants to switch from maintenance with peanut flour to actual peanuts, and one has to question the morality of the NHS paying £10.12 per day for two peanuts for each child on maintenance therapy with Palforzia.

Twelve months of Palforzia for one child will be costing the NHS £3693.80 (+VAT). The cost to the NHS to provide challenge capacity, appropriately trained staff to supervise the up dosing and food challenges is considerable. Palforzia treatment in the NHS is therefore likely to be made available to a relatively small number of children, predominantly confined to well-resourced tertiary paediatric allergy centres.

Schofield submitted his case report to the Lancet with his affiliation listed as Harley Street. He does not record how much he charged for either his pills or his service or how many visits had to be

made to his Harley Street practice during the course of the immunotherapy. A century on, a small minority who have the ability to pay, will seek treatment in the private sector.

However, the fundamental concern is that whether the treatment is being offered in the NHS or privately, a thorough discussion takes place of the many issues related to peanut immunotherapy: adverse events requiring AAI administration; the potential as immunotherapy use becomes more widespread for occasional episodes of life-threatening anaphylaxis, as with the Spanish experience; long-term potential side-effects, including eosinophilic oesophagitis; equivocal quality-of-life data; ongoing tolerance requiring sustained and potentially life long consumption; treatment not allowing any additional peanut consumption beyond the Palforzia itself; extensive cofactor restrictions (no exercise or hot bath or shower immediately before or for 3 hours after taking a dose, no alcohol to be taken from two hours before or two hours after a dose; dose recommended to be taken in the evening but not taken within 2 hours of bedtime; dosage adjustment to be considered for 'menstruation', 'stress' and 'fatigue or sleep deprivation').

The first paper to assess real-world adoption of peanut immunotherapy with Palforzia found that of 237 peanut-allergic individuals, 22 (9.3%) chose to pursue peanut immunotherapy with Palforzia, whereas 215 (90.7%) declined therapy.⁹ The two most common reasons to decline therapy were 'concern over adverse effects', and 'concern over the degree of commitment', cited by 35.4% and 28.5% of responding families, respectively.⁹ Significantly, children age 8–12 years and caregivers with low quality of life as reported by their FAQL-CF were more likely to pursue therapy with Palforzia.⁹ So potentially what improvements are being presented as occurring after successful peanut immunotherapy reflect a selection bias of those with significantly reduced quality of life at baseline. The question, therefore, is whether for the majority with higher baseline quality-of-life scores, is consideration of peanut immunotherapy even necessary?

CONFLICT OF INTEREST

The authors have no conflict of interest to declare in relation to this work.

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How to cite this article: Perkin MR. Palforzia for peanut allergy: Panacea or predicament. *Clin Exp Allergy*. 2022;00:1-3. doi:[10.1111/cea.14145](https://doi.org/10.1111/cea.14145)