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Therapeutic Advances in Peanut Allergy

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Peanut is the most common cause of food-related anaphylaxis in children, persisting into adulthood, unlike egg and milk allergy. Management of peanut allergy (PA), traditionally requires implementation of strict avoidance measures and perpetual emergency preparedness. This is burdensome for families leading to food anxiety, social exclusion and impaired quality of life[1]. Irish birth cohort data (2011-2013) show 1.9% (1200) of Irish infants, annually, develop PA. As around 80% of cases persist through childhood, it is estimated that around 20,000 Irish children have PA and at least a similar number of Irish adults are also affected.

The Learning Early about Peanut Allergy (LEAP) trial confirmed early introduction of dietary peanut for high-risk infants (severe eczema, egg allergy) between 4-11mths of age, reduced the relative risk of peanut allergy at age 5yrs by 81%[2]. PA also occurs in children in the absence of known risk factors, supporting a population-based approach to early allergen introduction[3]. Screening for peanut sensitisation prior to introduction remains controversial as sensitisation does not equate to true allergy and acts to delay peanut introduction as infants await hospital based peanut challenges. In Australia, where national feeding guidelines encourage early weaning without prior screening, 90% of infants ingest peanut[4]. In the US, initial "post-LEAP" guidelines advised screening of high-risk infants[3]. Recent data from the US, now shows an increase in both screening and in the prevalence of PA <12mths. A recent expert consensus recommends home introduction of allergens, including peanut, for all children regardless of level of risk, with the exception of families with a strong preference for screening, who are likely to otherwise delay introduction[5]. The success of introduction is markedly time sensitive, with better rates achieved in the youngest[6]. LEAP participants ingested peanut 3 times weekly until age 4. Follow-up shows persistence of tolerance 12 months after discontinuation. Tolerance is defined as sustained immunologic changes allowing ingestion without symptoms, in the absence of ongoing therapy.

Natural acquisition of tolerance is achieved in as few as 20% children and adolescents with confirmed PA. This has prompted widespread research into allergen-specific immunotherapy (AIT), the goal of which is to reduce clinical reactivity through gradual exposure to increasing doses of allergen. The efficacy of any immunomodulatory intervention has to outweigh the risk of inducing life threatening adverse reactions. Subcutaneous immunotherapy, although effective in inducing aeroallergen and insect venom desensitisation, triggered an unacceptable number of severe reactions when used as a route to deliver food allergens such as peanut[7].

Peanut oral immunotherapy (POIT) has, to date, been the best studied approach[8]. This process of desensitisation begins with a rapid escalation followed by an up-dosing phase during which increased doses of peanut are ingested under supervision at 1-2wk intervals, then repeated daily at home. On achieving optimum maintenance doses, daily ingestion continues indefinitely. In vitro changes include a rise in peanut specific IgG4 and a corresponding fall in sIgE levels. Over the past decade, studies have demonstrated, conclusively, that POIT effectively increases the threshold of reactivity to peanut. Efficacy and safety have been demonstrated across childhood from infancy to adolescence. A similar effectiveness is seen with high (3-4.5g approx. 12-15 peanuts) and low (300mg/approx. 1 peanut) maintenance doses but with less adverse events using the latter. The largest studies have been in the form of clinical trials examining the efficacy of a pharmaceutical-grade peanut powder preparation (AR101). The PALISADE and the ARTEMIS trial were multicentre (US, Ireland, UK, Europe, Australia), double-blind, randomised, placebo-controlled phase 3 trials (RCT) collectively involving over 750 participants. Across both studies, the median tolerated dose of peanut protein increased from 10 mg to 1000 mg(equivalent to 3-4 peanuts) between the entry and exit food challenges after a maintenance dose of 300mg[9,10]. On foot of these studies, Palforzia® has been licensed by FDA and European Medicines Agency(EMA) for the treatment of PA for children 4-17yrs. Meta-analysis of OIT trials have identified an increased risk of anaphylactic reactions over avoidance, however, these occur primarily during up-dosing[11]. Eosinophilic oesophagitis is a known risk, affecting maybe 1% of people on POIT. Quality of life measures show a positive impact on parents and participants due to the overall improved perception of risk in social environments. Discontinuation of daily exposure is associated with a waning of sustained unresponsiveness, as POIT does not induce tolerance. It is still not clear how long treatment should be continued. Some treated patients may prefer to stay on drug-grade peanut OIT, but others may prefer to transition to peanut containing foods. Pre-treatment and adjunctive treatment with the anti-IgE monoclonal antibody omalizumab, can shorten time to desensitisation and reduce risk of anaphylaxis. Dupilumab, an anti-IL4 receptor alpha antibody, is also being studied as an adjunct therapy. Many peanut allergic subjects are not exquisitely dose sensitive and this high dose tolerance can be exploited successfully with OIT at home[12].

Sublingual immunotherapy (SLIT) is a well-established route for desensitisation to aeroallergens such as grass pollen. SLIT food allergen treatment doses are1000 times less than those required for OIT, thus reducing severity of adverse events. A randomised placebo-controlled clinical trial involving peanut SLIT, demonstrated a 10-fold increase in the amount of peanut tolerated after 44 weeks of treatment[13]. To date, head-to-head comparison studies of OIT and SLIT show OIT to be more effective in that the final dose tolerated is significantly greater[14].

Epicutaneous immunotherapy (EPIT) involves the application of a Viaskin® adhesive dermal patch containing 250ug of peanut. Peanut is delivered to epidermal Langerhans cells, in turn promoting the proliferation of T-regulatory cells. In PEPITES, an RCT of children aged 4-11yrs, the difference in response rate, after 12mths compared with placebo, was 35.3% vs 13.6%, with minimal adverse events and high rates of treatment adherence[15]. After 3yrs follow up, the median cumulative reactive dose had increased from 144mg (equivalent to 1/3 peanut) to 944 mg (3-4 peanuts)[16].

Currently, none of the treatments detailed above are available in Ireland. The Viaskin® patch is currently not licensed for use anywhere outside research settings. OIT with Palforzia® is expected to start in Europe in 2022. Significant resources will be required to provide the obligatory baseline oral food challenge and approximately 20 day ward visits during the first year of treatment. AIT for food allergy should only be provided in tertiary care centres, equipped with the experience to counsel candidate patients and the skill set to proceed with desensitisation and respond to reactions.

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S.L. has no conflicts of interest to declare.

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