Position Paper - Oral Immunotherapy for Food Allergy

Key points

- Oral immunotherapy (OIT) is a potential treatment for food allergy. OIT is effective at inducing desensitisation but there is limited evidence if it can induce sustained unresponsiveness (remission) of food allergy.
- Food allergy OIT involves giving food allergens under medical supervision, initially in small amounts, then gradually increasing amounts, followed by continued daily consumption of the food allergen.
- If the goal of desensitisation is reached, there is a temporary increase in the amount of food allergen that can be consumed before an allergic reaction occurs.
- At present there is no evidence that OIT it is a cure for food allergy and there are no food allergy OIT products approved or registered by the Therapeutic Goods Administration (TGA) in Australia or by Medsafe in New Zealand.
- One OIT product that desensitises children with peanut allergy (Palforzia™ developed by the company Aimmune Therapeutics) received Food and Drug Administration (FDA) approval for use in the USA in 2020.
- There are no approved treatments that induce sustained unresponsiveness (remission) or tolerance.
- Food allergy OIT is an emerging treatment, and there are currently several clinical research trials of food allergy OIT and other treatments for food allergy underway in Australia and other countries.
- In some trials, food allergy OIT is combined with another component (co-treatment) that may help to make allergic reactions less severe, improve safety and encourage tolerance.
- The trials aim to develop standardised and proven methods to maximise benefit and reduce the risk of potential harm in people with severe food allergy. These trials are all hospital based due to high rates of allergic reactions.
- More data needs to be collected about safety, tolerability, cost-effectiveness, quality of life and long-term outcomes.

Food allergy

Food allergy occurs in around 5-10% of children, and 2-4% of adults in Australia and New Zealand. The most common foods that cause allergic reactions are egg, peanut, cow's milk (dairy), tree nuts, soy, sesame, wheat, fish and other seafood (crustaceans).

Whilst some food allergies result in mild to moderate allergic reactions, there has been a significant increase in potentially life-threatening severe allergic reactions (anaphylaxis) to foods in recent years.

Food allergies may be 'outgrown' with time:

- Studies have shown that while 11% of 12-month-olds have a challenge-proven food allergy
- Only about 4% of children still have their food allergy at four years of age.
- Peanut, tree nut, seed and crustacean allergies are less likely to be ‘outgrown’ and tend to be lifelong allergies.

However, when food allergy develops for the first time in adults, it usually persists.

Possible benefits of food allergy OIT are desensitisation and sustained unresponsiveness (remission)

Published trials show that food allergy OIT can result in desensitisation in many people, however only a subset may be able to achieve sustained unresponsiveness. Oral tolerance has not been shown.

There are three possible benefits of food allergy OIT:

- **Desensitisation** is a temporary state that allows a person to consume more of the food allergen than they could prior to OIT, but the underlying food allergy is still present so patients must still continue with strict allergen avoidance. Desensitisation requires the food allergen to be consumed regularly, without stopping, to maintain protection. Importantly, the level of protection is unstable so patients can react to their daily desensitisation treatment. The benefit to patients is protection against accidental exposure to small amounts of food allergen, while they continue on daily maintenance dosing (indefinitely) and adhere to strict allergen avoidance outside of their daily dosing.
- **Sustained unresponsiveness (remission)** means that a person can consume a larger amount of food than they could tolerate before treatment without having an allergic reaction, after having paused treatment for a period of several weeks. Typically, the patient is able to tolerate a standard serve or pass a diagnostic food challenge weeks after treatment discontinuation. The benefit to the patient is that they are able to introduce the food into their diet freely and no longer have to adhere to strict allergen avoidance. There is also no need for regimented maintenance dosing once the treatment course is completed.
- **Tolerance** means that a person can consume standard serves of the food allergen after a long period of avoidance or stopping OIT, for example even after years, without having an allergic reaction. This is similar to naturally occurring tolerance. There is almost no evidence regarding tolerance as an outcome of OIT.

Recent publications provide a comprehensive review of OIT for peanut allergy

Two recent publications have provided the most comprehensive and rigorous reviews of OIT for peanut allergy to date.

The first was a meta-analysis (a method to combine data from multiple studies) of 12 peanut OIT trials published in the Lancet journal in April 2019. It reviewed the effectiveness and safety of desensitisation with peanut OIT compared with peanut avoidance, combining all the studies where children with peanut allergy had been randomly assigned to either eat peanut or avoid it (control group). There were 1,041 children in these studies, with approximately two thirds taking peanut OIT and the remainder acting as controls.

Results showed that whilst peanut OIT can achieve the goal of desensitisation for many people, those who were desensitised with peanut OIT had more frequent allergic reactions, including severe allergic reactions (anaphylaxis). They also required more frequent treatment with adrenaline (epinephrine) autoinjectors (such as EpiPen®) than patients who avoided peanut and did not receive peanut OIT. The study also found that there is currently no evidence that desensitisation with peanut OIT improved patient quality of life.

Taken together, the findings of the Lancet publication suggests that desensitisation may not be an optimal outcome for patients and supports the need for improved food allergy treatment approaches with an enhanced safety profile and trials focused on improving patient-important outcomes such as quality of life. ASCIA also supports this approach.

Another meta-analysis that was published in Scientific Reports in January 2020 analysed the same 12 controlled studies and an additional 15 non-controlled studies. These 27 studies involved 1,488 children receiving peanut OIT. This analysis showed that certain aspects of treatment programs could increase the risk of anaphylaxis, while the inclusion of another component (co-treatment) may reduce the risk. This analysis also highlights the lack of data collected to date around patient-important outcomes such as protection from accidental reactions for those who have undergone peanut OIT in the past.

Both publications indicate that more research is required to identify effective OIT approaches for treating food allergy that are safer and provide longer lasting protection than current approaches.

Safety issues - food allergy OIT

It is important that people with food allergy and their families are aware that most food allergy OIT methods are not currently standardised or approved for routine treatment of food allergy globally.

There are currently no food allergy OIT products for food allergies approved or registered by the TGA in Australia or Medsafe in New Zealand. One OIT product for peanut allergy (Palforzia™ developed by the company Aimmune Therapeutics) received FDA approval for use in the USA in 2020. This form of OIT uses standardised amounts of peanut allergen powder contained in capsules.

Food allergy OIT safety issues include:

- Recent publications have shown that food allergy OIT leads to more allergic and adverse reactions compared with placebo or allergen avoidance (current standard care).
- People who are on food allergy OIT who achieve desensitisation but not sustained unresponsiveness (remission) can still have allergic reactions due to accidental exposure, or due to the OIT itself.
- There may also be other complications of food allergy OIT. For example, eosinophilic oesophagitis (EoE)* is more common in people with food allergies and is a contraindication to food allergy OIT. Food allergy OIT may make EoE worse, or EoE can develop in patients who did not have EoE prior to food allergy OIT.

*EoE is an immunological eosinophil-predominant inflammation of the oesophagus causing symptoms of oesophageal dysfunction. It requires upper GI scope and biopsy to make a diagnosis and generally requires treatment with food elimination and or corticosteroids.

Potential benefits versus safety issues and quality of life need to be considered. For example:

- If food allergy OIT results in **sustained unresponsiveness (remission)**, then the benefits may outweigh any other issues.
- If food allergy OIT results in **desensitisation**, the benefits are limited to protection against trace amounts. The food allergen still needs to be avoided, daily dosing is required and allergic reactions can occur as a result of these doses, all of which make it unlikely that there is a substantial improvement in quality of life.

Considerations prior to commencing food allergy OIT

Food allergy OIT should be given in a consistent way, to maximise its chances of effectiveness and minimise the risk of side effects. Being in a food allergy clinical research trial usually requires frequent visits to hospital, possible food challenge to the allergen before commencing food allergy OIT, blood tests and other investigations over many months or years.

Therefore, being in a food allergy OIT clinical research trial may present difficulties for people who plan to go on holidays, overnight excursions, camps, or board overnight at school. There will also be some inconveniences, potential costs (such as travel and time off work), lifestyle disruptions and restrictions that need to be carefully considered and these may vary widely for different age groups.

Each dose of food allergy OIT carries a risk of an allergic reaction, including anaphylaxis, so taking on responsibility for dosing a school student taking food allergy OIT cannot be expected of every school. When students are on overnight school excursions or camps, there can be changes in sleep patterns, busy activity schedules, lower ratios of carers to students and remote or unfamiliar locations. There are also increased risks of an allergic reaction with OIT doses for a person who has an infection, poorly controlled asthma or allergic rhinitis. These are all factors that can increase the risk of an allergic reaction with a dose of food allergy OIT.

Therefore, people on food allergy OIT may need to choose between attending school activities and interrupting OIT, depending on discussions with schools and camps or other factors. These factors should also be considered for people going on holidays or other activities with their family or friends.

There are added risks when food allergy OIT is recommenced after a long interruption. For this reason, the OIT clinical research trial doctor or treating clinical immunology/allergy specialist may recommend that this occurs in a supervised medical setting, in a similar way to a food allergen challenge. There are often long waiting times to access food allergen challenges outside of research settings. Therefore, a treating clinical

immunology/allergy specialist may not be able to offer rapid access to a suitable setting for recommencing food allergy OIT when interruptions occur.

All patients and participants in food allergy treatment clinical research trials should remain under the regular care of a clinical immunology/allergy specialist. They play a particularly important role in ongoing management decisions once a patient finishes a clinical research trial, in consultation with the patient's GP.

Food allergy treatments offered in clinical research trials may not be available for participants when the trial finishes. It is important for patients to discuss tentative plans for management after the trial with their regular clinical immunology/allergy specialist when deciding whether to participate in a clinical trial.

Current ASCIA recommendations for management of food allergy

Until food allergy OIT and other treatments for food allergy are proven to be effective, safe and standardised for routine use, and approved by regulatory bodies (such as FDA, TGA or Medsafe), strict avoidance of confirmed food allergens is recommended for the management of food allergy.

All patients receiving food allergy OIT (Palforzia™ or other OIT administered as part of a clinical research trial) should be advised of the increased likelihood of allergic reactions (including anaphylaxis) and be prepared for these events. They should continue to be managed in conjunction with their regular clinical allergist/immunologist.

It is important for people with food allergy and their families to:

- Know the signs and symptoms of mild to moderate allergic reactions and anaphylaxis.
- Know what to do when an allergic reaction occurs.
- Read and understand food labels for food allergy.
- Inform wait staff that they have food allergy when eating out.
- Be aware of cross contamination and contact with food allergens when preparing food.
- Carry their adrenaline autoinjector (if prescribed), and their red ASCIA Action Plan for Anaphylaxis.

Further information and support

Lancet publication: www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)30420-9/fulltext

Scientific Reports publication: https://doi.org/10.1038/s41598-019-56961-3

Information about food allergy: www.allergy.org.au/patients/food-allergy

Information about venom or aeroallergen immunotherapy: www.allergy.org.au/patients/allergy-treatment

Patient support:

Allergy & Anaphylaxis Australia www.allergyfacts.org.au or Allergy New Zealand www.allergy.org.nz

For more information go to www.allergy.org.au

To donate to immunology/allergy research go to www.allergyimmunology.org.au