Oral Immunotherapy for Ig-E mediated Food allergy: in practice

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Abstract

Oral immunotherapy (OIT) is a treatment that can be proposed to food allergic patients with very favorable results, especially in the short-term. OIT consists of administering the food allergen in progressively increasing amounts attempting to reach a normal dose. Guidelines vary from country to country. EAACI recommends OIT for children over five years of age with a persistent allergy to cow's milk, egg and peanut. In Spain and Canada, it is proposed for any age and any food. Since adverse events are always possible, the patient and his family must be well trained to manage these allergic reactions. The aim of OIT is to improve the quality of life of these patients by increasing the reactogenic threshold or in the best cases, by attempting to achieve a state of desensitization or tolerance to the allergen.

Introduction

Food allergy concerns recently 4-8% of the children of the United States and Europe, and the prevalence of anaphylaxis in Europe is around 0.3% (1-4). We observe an increase of severe anaphylaxis in the last years in the western countries, especially in children under 5 years old, without an increase of mortality (2). Severe anaphylaxis appears essentially with allergies to cow's milk (CM) and eggs under 2 years old, cashews nuts and hazelnuts under 6 years old and peanut for all ages (2, 4). Approximately 80% of CM and egg' allergies outgrow naturally as children grow, while only 15 to 20% of nut and peanut allergies outgrow naturally. This motivates allergists to find a way to help those patients who do not naturally become tolerant (3-5). Accidental exposure is also not so rare: in the USA, the annual incidence rate of accidental peanut ingestion is between 12 to 23% while in Japan, 17-36% of CM allergic patients and egg allergic patients have been exposed accidentally (4). The standard care to treat allergy is, for the moment, allergen avoidance and rescue treatment (antihistaminic and epinephrine) (3).

Oral immunotherapy (OIT) seems to be an interesting solution. It consists of giving daily a dose of allergen to an allergic patient, starting with a very small and tolerated dose, which is increased monthly, until attempting a normal dose for that allergen (for example, a cup of 200ml of CM). The goal of OIT is for the patient to become tolerant to the allergen, but most of the time this state is not achieved and patients become desensitized. Tolerance and desensitization (or "sustained unresponsiveness") are two different concepts that are important to understand. Tolerance means that the patient is able to eat the allergen without symptoms, even if he does not eat it regularly. Desensitization is a step below tolerance: the patient needs to consume the allergen without discontinuation to maintain a non-allergic response to that allergen. Desensitization is most often the state achieved at the end of OIT (1, 4). By achieving desensitization or tolerance, OIT reduces the risk of allergic reactions, especially anaphylaxis, in the event of accidental exposure. For example, in peanut allergy, it reduces the risk of mild allergic reaction by 12% per year and the risk of anaphylaxis by 7% per year (3).

The roles of the allergologist before OIT were to diagnose the allergy, to explain the avoidance regime, to educate the patient to notice the allergic reaction symptoms and to treat them. Avoidance regime may cause stress to the patient and his entourage, accidental reaction, nutritional deficiency and so on. With OIT, the allergologist is able to cure his patient and allow him to avoid the above mentioned embarrassments.

Oral immunotherapy (OIT)

A. OIT: Which patients are concerned?

In 2018, the EEACI recommends OIT only for patients from 4 or 5 years of age with persistent Ig-E mediated allergy to egg, CM and peanut (1). They do not recommend it for other food because it has been not enough studied for now. As more studies on OIT for other foods are found, these recommendations might change in the future.

In Canada and Spain, OIT can be offered to any patient with a food allergy, for any food, even in the context of multiple food allergies and for adults (4).

Patients and their families must be correctly selected. Indeed, patients must have a clear history of allergy with an acute reaction, have a positive skin prick test and/or specific Ig-E for the allergen and pass an oral food challenge (OFC) to confirm the allergy and to evaluate the reactive dose (1). The family should be well informed about the type of protocol, the type of side effects that may occur during treatment, the rigor and length of time that this type of processing may take. Only very motivated and awarded families should start these protocols (1, 4).

Patients who have great chances to outgrow their allergy naturally (allergy for CM and egg in particular) should not be treated with OIT (1).

Some contraindications are summarized in Table 1, some of them are absolute and others more disputable (1, 4, 6).

Table 1: Contraindications to oral immunotherapy.

Absolute Contraindication
Uncontrolled asthma
Low family compliance
Neoplasia or autoimmune disorders
Eosinophilic esophagitis
Non Ig-E allergy
Relative Contraindications
Pregnancy
Chronic urticaria, severe eczema
Beta-blockers or ACE inhibitors use
Active mastocytosis

Figure 1: Classic protocol of OIT.

B. OIT: Classic protocols and practical recommendations for the patients

As shown in Figure 1, a classic OIT protocol would begin with an OFC to prove the allergy. This OFC also allows the reactive dose to be determined. The first OIT dose will correspond to 1/10th of the reactive dose to make sure no reaction would occur at home. The next doses are generally increased every 2 to 4 weeks until the final dose is reached. Every first increased dose is given in the hospital under medical supervision (4, 7). Then the dose is consumed every day at home for 2 to 4 weeks according to the protocols. When the final dose is reached, the patient enters the maintenance phase (7).

The daily dose consumed at home must be taken according to certain rules: it must be taken at a regular time, under parental supervision (not before nap time or night time), with food (snack or meal), without exercise 1 hour before and 2 hours after (1, 7).

Some situations may increase the risk of allergic reactions during OIT, such as fever, exercise, stress, NSAID or alcohol use, uncontrolled asthma. In these cases, OIT should be suspended until the patient is in a normal state. The protocol may change if the break is too long: the allergist may suggest restarting it at a lower dose for a while (1, 7).

Parents and family should be well trained and equipped to manage the potential reactions during OIT (7).

To prove that the patient has become tolerant to the allergen, the patient should pass another OFC after an eviction period at the end of the maintenance phase. The duration of the eviction phase is not well defined in studies and can vary between 4 weeks to several months. If the OFC is positive at that time, the patient has become desensitized but not tolerant (6).

C. OIT: Side effects

Allergic reactions are extremely frequent during OIT (about 80% of the patients), which is even more than with the eviction diet. Most of the side effects occur during the build-up phase or in association with cofactors (fever, sport, pollen season…) (7, 8). Most of them are mild or moderate reactions, such as perioral rash, urticaria, rhinitis or mild gastrointestinal reaction. Most of them resolve with antihistamine treatment or even by themselves (8). Anaphylactic reactions can also occur, affecting approximately 25% of patients in the studies (3, 7). Kansen et al. followed patients under avoidance in real life for 3 years and concluded to an annual risk of anaphylaxis of 9.8%. None of these patients used epinephrine as it was proposed to do in such situations. Chu et al. found a lower rate of severe reactions in avoidance patients (2.7%) but this was in a clinical trial population that was more strictly followed medically (3, 9, 10). Eosinophilic esophagitis is also a side effect in 0.5% to 5% of the cases and requires discontinuation of OIT treatment. Hopefully, the situation is reversible when the contact with the allergen is discontinued (7, 8).

Given the possibility of developing anaphylaxis during OIT, the whole procedure must be supervised by a center with a high food allergy expertise and full resuscitation equipment (1).

On the long term, the mild side effects can be a barrier to the treatment of patients who eventually end OIT due to the discomfort of these side effects (7, 8). The discontinuation rate of OIT can be as high as 14% according some studies (8). Fatigue and aversion to food may also reasons for treatment discontinuation (7).

A meta-analysis on peanut allergy, published in The Lancet in 2019, confirmed these prerogatives of side effects. They included 12 RCTs with a total of 1041 patients (medium age 8 years, 39% girls and 61% boys). The control group were patients with placebo OIT (8 studies), patients under avoidance (3 studies) or patients ongoing sublingual immunotherapy for a food allergy (SLIT) (1 study). The median final dose was 2000 mg of peanut. There was no OFC at the beginning of each study. The OIT groups showed an increased risk of anaphylaxis with a RR of 3.12 (95% IC 1.76-5.55) and an increased epinephrine use with a RR of 2.21 (95% IC 1.27-3.83), both in the build-up and the maintenance phase. Non-anaphylactic reactions were also increased in the OIT groups: vomiting (RR 1.79 with 95% IC 1.35-2.38), angioedema (RR 2,25 with 95% IC 1.13-4.47), upper respiratory tract reactions (RR 1.36 with 95% IC 1.02-1.81), lower respiratory tract reactions (RR 1.55 with 95% IC 0.96-2.5). Trials, which had not done an OFC at study entry, had a 2.68-times lower risk of anaphylaxis during OIT than the other studies. No patients died in any of the studies. Only 3 cases of eosinophilic esophagitis were reported (3). The biggest difference between side effects that would occur during an eviction diet and during an OIT protocol is that, in the second situation, side effects can be expected: the patient is under parental supervision, medication is available and the parents have been well trained to react. In the eviction diet situation, the accidental exposure occurs mainly when patient is not at home, with absence of rescue medication, or under the supervision of a non-well-trained adult (10).

D. OIT: Does it work?

EAACI has conducted the largest review on the efficacy of OIT in 2021. They reviewed 18 randomized and controlled trials (RCT) and 5 controlled clinical trials (CCT) with a total of 982 patients allergic to egg, cow's milk or peanut. They excluded other foods because they have not been sufficiently studied at that moment. The authors concluded that OIT gives good results. A majority of patients (76.9%) tolerated the expected dose of food at the end of the protocol, regardless of the type of protocol (e.g. dose escalation which can vary from one study to another) or the type of food, compared with 8.1% in the control group. Four of these studies (25 patients allergic to CM and 169 to eggs) statue on the medium-term efficacy of tolerance by testing patients with an OFC after a period of avoiding the food. The period of avoidance

was quite short: between 1 and 3 months, which does not allow us to conclude to a real tolerance in the long term. This is nevertheless a recurrent problem in most studies: the tolerance status is often unknown. The conclusion of this review did not really change from the one of 2018: OIT is indicated for children from 4 or 5 years of age with persistent allergy to CM, eggs or peanuts and OIT is effective. EAACI does not currently recommend OIT for other food or for adults due to lack of evidence (1).

Two Cochrane meta-analyses showed almost identical results. The first one is on 10 controlled trials (3 with placebo, with a total of 249 patients) on egg's allergy where desensitization was obtained in 82% of patients, versus 10% in the control group. The second meta-analysis included 196 children from 5 randomized trials on cow's milk allergy: 62% became desensitized in the OIT group versus 8% in the control group (4).

But, according to certain trials, OIT might be more effective in younger children (under 5 years of age) than in older children. This has been lately illustrated in 2 studies.

The first one is a real-life study published in 2020, without any control groups or randomization, on peanut allergy, in a cohort of preschoolers (9-70 months old). Children were required to have a positive OFC for peanut or a clear history of peanut allergic reaction and a positive skin prick test or positive level of specific Ig-E for peanut. The build-up phase was short (16 to 22 weeks) to achieve the maintenance dose of 300 mg. Eventually, after a maintenance phase of 12 months, 117 patients (mean age = 25 months, 59.8% boys) completed the protocols and passed the final OFC. Ninety-two of 117 patients (78.6%) succeeded this test and tolerated cumulative dose of 4000 mg peanut protein and 115 of 117 (98.3%) were able to tolerate a cumulative dose of 1000 mg peanut protein. The skin prick test decreased significantly more in the successful OFC group than in the group that still had a positive OFC (43.5% vs 20.2%, $p<0.05$). They didn't find a significant difference in the decrease of Ig-E in these 2 groups. This study shows that nearly all patients can achieve the protective dose of 1000mg, which according to other studies provides protection against accidental exposure. Side effects were also very low: 9.5% had an allergic reaction (grade 1 and 2) and 1.6% received epinephrine during the maintenance phase (10).

The second study in a young population is a multicenter RCT in children aged 1 to 3 years. The 146 enrolled children passed at first a double blind, placebo-controlled OFC and had to have a reaction to 500mg of peanut or less to participate to the study. 96 patients received peanut OIT (2000 mg peanut protein per day) and 50 patients received placebo for 134 weeks; then they all achieved a period of peanut avoidance for 26 weeks. In the per-protocol analysis, at week 134, a first OFC showed that 84% (68/81 patients; 15 patients dropped-out) of the peanut group passed the challenge (with a median dose of 5005 mg of peanut protein) and only 3% (1/35 patients; 15 patients dropped-out) of the placebo group (risk difference 69%, 95% CI 59-79; $p<0.0001$). After the avoidance period (week 160), in the per-protocol analysis, 29% (20/70 patients; 11 patients dropped-out) of the peanut group succeeded the challenge compared to 4% (1/23 patients; 12 patients dropped-out) in the placebo group (RD 19%, 95% CI 10-28; $p=0.0021$). This time, the median dose of peanut protein in the non-placebo group was 755mg. However, 57% of these children (40/70 patients) were able to consume 1755-3755 mg of peanut, which is a safe level for accidental ingestion. Another surprising result is that the chance of tolerance success is higher when the patient is young: in fact, 71% became tolerant in the group younger than 24 months (although this group was quite small, 12% of the population), 35% between 25 and 34 months and 19% between 36 and 48 months. Most participants in both groups experienced side effects during the study (98% in the peanut group and 80% in the placebo group). The reactions were mild to moderate and 35 moderate reactions were treated with epinephrine (only in the peanut group) (11).

Compared to study on peanut allergy in older children, the results of the study in young children are slightly better. Effectively, the POISED study shows that 20% of the patients (median age 11 years) were able to consume 4000 mg of peanut after an avoidance period of 26 weeks (11).

E. OIT: impact on quality of live

Some studies have investigated the impact of OIT on the quality of live (QoL) of patients undergoing OIT. Goldberg et al. showed a significant improvement in QoL in the OIT-treated group (56 patients) compared to the placebo group (47 patients) ($p<0.001$) (12). Levy et al. have studied a population of 191 patients between 4 and 12 years undergoing OIT and have shown an improvement in QoL in terms of emotional and social impact and a reduction in stress related to food consummation. Some of them reported a decrease in QoL during OIT, but an improvement of it at the end of an OIT protocol (13). So far, studies about QoL on the long term are missing.

These studies remind us of the importance of correct selection of patients and their families for such a protocol. The patient should be aware of his wishes regarding the evolution of his allergy and should be well informed about the impact of these protocols on his life.

F. OIT: Open questions

A lot of questions concerning OIT are still without any answer for the moment. Therefore we need more studies. What is the long-term efficacy of OIT? When can we consider a patient to be tolerant? Is it possible to establish a standardized protocol or do we need an individual protocol for each patient? What is the impact of OIT on long-term QoL? Can we find safe biological markers of OIT efficacy? Can we use other drugs to improve OIT response (omalizumab, probiotics,…)? What is the ideal age to start OIT?

Conclusion

We can conclude that OIT can be proposed to selected patients with a permanent food allergy. The patient and his family should be well informed and motivated. Side effects are more frequent than in an eviction diet, but parents are well-equipped and well-trained to react to them. The short-term efficacy of OIT has been proven. We still have a lot to learn about this topic and we hope to have more answers to the remaining questions in the future.

Conflicts of interest

The author has no conflicts of interest to declare with regard to the topic discussed in this manuscript.

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