Current trends in pediatric food oral immunotherapy - early start, low dose and long maintenance, multi-food protocols

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Abstract

Background: Oral immunotherapy (OIT) has been the best studied therapeutic approach for the treatment of food allergy over the past decade, with clinical trials evaluating its efficacy, safety and ability to improve participants' quality of life.

Methods: In this article we review trends in the evolution of treatment regimens, beneficial and side effects of current OIT protocols for single or multi food allergy. We report the conclusions drawn from the publication of some studies and a meta-analysis that highlighted the drawbacks of OIT, as well as studies concerning multi-food oral immunotherapy.

Results: OIT protocol with a low maintenance dose, slow progression, early onset even at preschool age and tailored to the severity phenotype has shown significant feasibility, efficacy and safety, offering a promising option for the management of patients with severe food allergy. Studies have also shown that a short course of omalizumab can safely accelerate the OIT schedule for multiple allergens simultaneously. Therapeutic education and informed shared decision-making between patients and the medical team are essential.

Conclusions: According to literature data and for reasons of safety, cost-effectiveness and logistics, OIT protocols are mainly aimed at single food allergy cases. This approach is becoming increasingly complex, as multiple food allergies (30% of cases) are generally more severe, have a greater impact on quality of life, and are less likely to resolve spontaneously over time. Future research should evaluate the short- and long-term effectiveness of this therapy in the real world, predictors of efficacy, and the use of adjunctive therapies that may mitigate adverse events.

Introduction

Due to the challenging evolution of food allergy in the last decade – oral immunotherapy (OIT) protocols have brought real benefit with relatively easy acquisition of desensitization. A recent systematic review showed that this approach is effective and to be associated with an 80% improvement in quality of life (1). In addition to the increase in prevalence, more and more severe phenotypes are being reported as food poly-allergy, polysensitization. Up to 30% of food allergic patients react to more than one food allergen. This estimate rises to 70% in highly atopic patients. These severe phenotypes appear very early in life, and their quality of life is severely compromised due to multiple and recurrent adverse reactions (AR). As a significant finding, the results of the Immune Tolerance Network IMPACT trial have suggested that early intervention with OIT can induce clinical remission (2). Many studies have also shown that it is possible to perform OIT to several foods simultaneously at preschool age. The main goal of OIT is to raise the threshold of reactivity in order to prevent severe anaphylaxis due to accidental ingestion of the allergen. Currently protocols are heterogeneous and vary, according to the type of food used (e.g., fresh or cooked, single or multi-food), the progression of doses, the amount of protein/maintenance dose, the duration of each stage and the adaptation of the protocol according to the phenotype.

The clinical efficacy of OIT is assessed by the increase in the threshold of reactivity to a specific food, consumption without ARs or clinical remission. In the past the high maintenance doses were considered effective in achieving clinical remission (3). This practice has been abandoned over time in the face of serious adverse reactions (SAR) at higher rates than with elimination diets. The development of remission is directly linked with immunological biomarkers. On the other hand, sublingual immunotherapy and epicutaneous immunotherapy have been reported to have acceptable safety and efficacy profiles, to be applied especially in severe phenotypes of interest as a transition to the OIT.

According to current studies, OIT with early onset (even before preschool age) adapted to the severity phenotype (slow progression, low maintenance dose), has shown significant efficacy and safety. Although OIT-related ARs are common during treatment, SARs are rare (1-3).

OIT protocols: maintenance doses, efficacy, adverse effects, MFOIT according to recent studies

To date, only the guidelines of the Canadian Society of Allergy and Clinical Immunology recommend OIT multi foods, while other scientific bodies recommend OIT only for peanuts, eggs and cow's milk. In the literature, the foods involved in OIT in small doses are milk, eggs, peanuts, wheat, nuts and a multi-food mix (up to 15). Therapeutic education, detailed information and informed shared decision making, between patient and the medical team, are essential. An early start is desirable for several reasons: better immunological plasticity, easily controllable co-morbidities, good acceptance given few food phobias (neophobias) and better protocol compliance due to parental support. Regarding timing and dosage: a lower allergen delivery dose and a slow, delayed escalation rate in OIT treatment seem approachable in the near future. Multifood oral immunotherapy (MFOIT) versus OIT has shown a real benefit in terms of protocol duration for polyallergic patients. In older children, it is essential to respect the patient's personal objectives: some may wish to be able to consume large amounts of allergens, while others may simply want protection against anaphylaxis in the event of accidental ingestion. Small maintenance doses vary from 125 mg to 300 mg of protein for peanuts and tree nuts. In other studies, the

doses were 3 ml of milk, 1/32 of a whole egg, 2 g of boiled noodles (4-6). Studies have also shown that a short course of omalizumab can safely accelerate the multi-food OIT schedule. There are still many unanswered questions regarding the optimal dosage, duration of treatment and evolution of OIT after omalizumab discontinuation.

Regarding the monitoring of OIT, some studies have shown that small skin test diameters and serum IgE (sIgE) at the beginning and end of the maintenance phase, in addition to reduced basophil reactivity, can predict the achievement of sustained unresponsiveness (SU), whereas IgG4 is not predictive of SU (7). Regulatory markers, in particular FOXP3 + and Tregs, appear to play a key role in the induction of long-term tolerance in therapeutically successful patients (8). The current hypothesis is that immune memory is allergen-specific; however, synergistic effects cannot be ruled out.

Lessons from different studies: arguments for early, low dose, long, multifood protocols

PEANUTS AND TREE NUTS

An Atlanta research team in 2017 demonstrated the efficacy of small maintenance doses after comparing 3000 mg vs. 300 mg of food protein (FP) in children aged 9-36 months. Thus, 78% of subjects achieved desensitization (300 mg arm, 17/20 [85%] vs. 3000 mg, 12/17 [71%], p=0.43) over an mean period of 29 months. Peanut IgE levels decreased significantly in the active group (AG) versus placebo group (PG) (p<0.001). Early OIT was safe and well tolerated with predominantly mild symptoms, a single home reaction requiring epinephrine and 2 withdrawals due to persistent gastrointestinal ARs (3). According to Kulis et al. no differences in T-cell or basophil responses were found between subjects on low-dose or high-dose maintenance peanut OIT. The risk of ARs and study withdrawal was higher in the high-dose group. These results suggest that lower maintenance doses are preferable in the long term (3, 9).

The PALISADE study, 2018 included patients (aged 4-55 years) with a history of severe anaphylaxis and a maximum cumulative reactogenic dose (CRD) of 100 mg FP. The induction phase, lasting around 6 months, aimed at a maintenance dose of 300mg FP. This was followed by a 6-month maintenance phase. OIT was effective in 496 patients aged 4-17 years (not in adults), with 67.2% of the AG tolerating a 600 mg dose after 6 months of maintenance compared to 4% of the PG. After 1 year of treatment, 50% tolerated 1000 mg FP. However, SARs occurred in 6% of the AG participants and less than 2% of the PG participants. Overall, systemic allergic reactions occurred in 53 patients (14.2%) in the AG and 4 (3.2%) in the PG. One patient developed an eosinophilic esophagitis (EoE) and 4.3% of the AG participants withdrew due to chronic gastrointestinal symptoms. [10]. The randomized, controlled PALISADE trial demonstrated the benefit of daily oral immunotherapy with peanut (Arachis Hypogaea) allergen powder (AR101) at a low maintenance dose in peanut-allergic children and adolescents (10).

German researchers in 2019 confirmed the efficacy of OIT (children aged 3 to 17 years, 31 in each group (AG/PG)) with a better safety profile due to a slower progression pattern and lower maintenance doses than in the PALISADE study. Dose escalation took place over a maximum of 14 months, followed by a 16-month maintenance period (30 mg FP). As a result, 74.2% of the AG tolerated at least 300 mg FP vs. 16.1% in the PG ($p < 0.001$). Mild to moderate ARs occurred in 90% of AG patients versus 77% of PG patients,2.17% of AG patients received epinephrine. The study found no differences between the groups in dropout rates (6.7% of ARs due to OIT), symptom severity and treatment, or worsening of pre-existing atopic diseases. In conclusion low-dose OIT to nuts at preschool age is safe and effective in the real world (11).

Canadian preschool peanut oral immunotherapy (CPPOIT) in 2020: this is the first group to describe OIT (mono- and multifood) in preschool age, a real-life multicenter study whose aim was to design a protective OIT with minimal risk. Among 270 children (aged 9 to 71 months), 90% achieved maintenance of 300-320 mg FP with an mean induction duration of 16-22 weeks. 36.3% of patients reported mild symptoms and 31.1% moderate symptoms (grade 2). There were 11 epinephrine administrations, or 4.10% of patients, 6 in the clinic and 6 at home. The limitations of this publication are related to the fact that this is a real-life study, with a lack of adherence to the protocol (no diary, so missed doses were not assessed). This lack of adherence induces a risk of ARs during OIT, hence the need for close education in the use of adrenaline (in this study, all 11 adrenaline injections were given for moderate reactions). There was no correlation between increased IgE antibodies and exit from the study. SARs were in the order of 0.4%, less than in the PALISADE study (4.3%), as was the use of adrenaline during induction: CPPOIT 4.07% versus PALISADE 14%. EoE was diagnosed in 1/270 patients (0.37%), similar to PALISADE. Asthma was not recorded as an AR in CPPOIT, which recruited preschoolers with mild/moderate asthma under optimal control, with the intention to minimize the risk of ARs and study exit (12).

The Grzeskowiak et al. 2020 meta-analysis: 27 studies (1488 subjects) of peanut OIT (large and small maintenance doses) in children under 18 years of age, charting ARs, ability to reach the target maintenance dose and success of OFC after OIT. They show that the risk of protocol interruption due to ARs is lower when co-treatment (AH, probiotics, omalizumab) is associated. After the stratified analysis the treatment with omalizumab proved to be superior to AH and probiotics. ARs were frequent and led to treatment discontinuation in 6.6% of children. ARs requiring epinephrine treatment occurred in 7.6% of participants, at a rate of 2/10,000 doses. Specific IgE levels and the presence of asthma were the main risk factors for treatment discontinuation observed in univariate meta-analysis.

The use of an initial rush phase was consistently associated with an increased risk of SARs, just as aiming for a higher target maintenance dose (above 1 g FP) was also associated with an increased risk of epinephrine use. The risk of SARs was identical during the rush, dose escalation and maintenance phases, but the frequency was higher during the rush phase. Although the risk of SARs requiring epinephrine treatment may seem high at 7.6%, this must be conveyed to the patient along with the excellent benefits of OIT in protecting against accidental allergen ingestion. According to this meta-analysis, once children have reached the long-term maintenance phase, the risk of a SAR requiring epinephrine treatment is 3.2%, while the frequency is extremely low, on the order of 9 episodes per 100,000 doses. In terms of objective analysis, failure to reach dose was more important in the high-dose protocols. The final oral food challenge (OFC) success was 68.9% in 17 studies (small and large doses), and was higher in studies that used co-treatment (probiotics or omalizumab, but not antihistamines (AH)). Only three RCTs examined the effects of different approaches to OIT. These include different target maintenance doses, the use of co-treatment (omalizumab vs. placebo) (4). These studies have provided encouraging evidence that a lower maintenance dose and the use of co-treatment may reduce the risk and frequency of ARs (4, 12).

A French single-center retrospective study in 2020, of 100 children (mean age five years) who received a hazelnut OIT. Maintenance was performed with 416 mg of hazelnut protein. After six months of treatment, 34% were successfully desensitized (tolerance of 1635 mg FP); patients with positive reintroduction tests were able to acquire an increased reactogenic dose. The proportion of desensitized patients increased as the maintenance phase was extended. Successful desensitization was associated with an earlier treatment initiation, a smaller hazelnut skin

test wheal diameter, lower hazelnut IgE levels, and absence of cashew nut allergy. The success of desensitization was not dependent on comorbidities (atopic dermatitis, asthma) or a higher level of Cor a 14 IgE. No SARs were associated with OIT (13, 14).

Israeli researchers in 2019 demonstrated the efficacy of OIT to walnuts at a maintenance dose of 1200 mg walnut FP. Of the 55 patients in the AG, 49 (89%) were desensitized to walnuts, compared to none of the 18 patients in the CG (p<0-0001). Following walnut desensitization, all patients who were co-allergic to pecan (n=46) were also desensitized to pecan. In addition, 18 (60%) of the 30 patients co-allergic to hazelnut or cashew, and 14 (93%) of the 15 patients co-allergic to hazelnut alone, were desensitized. 47 (85%) of the 55 patients had an adverse event (mainly grade 1 or 2) when the dose was increased in the clinic; eight patients required epinephrine in response to a home dose. According to this study, walnut OIT can induce desensitization to walnut as well as desensitization to pecan and hazelnut in patients co-allergic to tree nuts. The safety profile is reasonable. A low daily dose of allergen maintained desensitization (15).

COW'S MILK, WHEAT

In a 2016 Japanese study, the OIT protocol included 403 subjects: 217 subjects for cow's milk (CM) (median age, 6.0 years; interquartile range, 3.8–9.3 years) and 186 subjects for wheat median age, 6.8 years; interquartile range, 3.3–9.3 years). The OFC for CM or wheat contained 3 mL heated CM (102 mg CM protein) or 2 g udon noodles (52 mg wheat protein), respectively. The low-dose OFC appears to be useful for confirming tolerance to low doses of causative foods and improving the prognosis after 1 year. Inclusion of low doses of causative foods in the diet of patients with a food allergy after a low-dose OFC may improve quality of life. Subjects who passed the low-dose OFC were advised to consume a food containing 3 mL of heated CM or 10 g of butter (equivalent to 2.9 mL CM) for CM allergy or 2 g of cooked udon noodles for wheat allergy at home at least once a week. Within 1 year after confirming the tolerance to the low-dose OFC, 45% (18/41) of patients were able to consume 25 mL of heated CM. With regard to wheat, within 1 year of confirming tolerance to 2 g of cooked udon noodles, 56% (18/32) of patients were able to consume 15 g of cooked udon noodles. Only a few patients had symptoms at home, 9.8% of those with CM allergy and 3.1% of those with wheat allergy, and the symptoms were not severe in any of the cases (16).

MFOIT- A PROGRESSIVE, REAL-LIFE PROTOCOL

A first study of MFOIT without omalizumab pretreatment was published in 2014 by Bégin et al. including up to 5 foods simultaneously in 25 patients, with the result that 22/25 patients were able to achieve daily doses 10 times greater than the initial reactogenic cumulative doses (RCDs) for each food (17).

In 2019, a Detroit research team enrolled 45 patients in an MFOIT. The foods included were peanuts, nuts and seeds. Most patients (76%) received an OIT for 4 or fewer foods, although a few patients had more foods (up to 12). Thirty-five patients started OIT on the basis of positive single-food OFC results; 10 patients started treatment on the basis of a history of anaphylaxis to the food (ranging from 1 to 12 years prior to starting OIT) and still remained positive on allergy testing. Three of these 10 patients had allergic reactions when the dose was increased. The mean time to maintenance was 24 weeks (range, 9-54 weeks). Six patients (13%) discontinued OIT. According to Eapen, MFOIT is feasible and safer than multiple food avoidance. Most patients can achieve a maintenance dose that provides good protection against reactions to involuntary food ingestion. Four patients reached the end of the protocol and continue to receive the food 3 times per week to maintain long-term tolerance. The OIT diet in this study was adapted to each patient for safety, tolerance and practical reasons to match real-life conditions. The final maintenance dose was also determined individually (18).

In a retrospective analysis (2020-2022) at CHRSM Namur of the medical records of 31 food-allergic patients (age 2- 10 years) who had received MFOIT(egg, peanut, nut, sesame), it was found that 87% (27/31) of patients tolerated 300 mg of protein from each food at the end of the protocol, thus protecting against most accidental exposures. The protocol included 6 months of induction and 6 to 18 months of maintenance, depending on the severity of the phenotype. 51% of patients passed the final OFC at 2g PF, and all patients increased the reactogenic dose by more than 15-fold compared to the initial RCD. ARs were predominantly grade 1 and 2 (Ring and Messmer). An initial OFC was performed for each food in the MFOIT (in the absence of anaphylaxis to the food concerned in the anamnesis or other elements with high predictive value for allergy), and the maintenance dose was 300 mg protein/food/day. In 4 patients, adrenaline was used during the maintenance period, in the context of cofactors or abdominal pain whose worsening was not notified to the physician.4 patients dropped out due to relocation, family separation and worsening of pre-existing food phobias. In our experience, low-dose MFOIT with a long maintenance period is an effective treatment option. It is essential to put in place the tools to guarantee good safety, such as -practice in specialized centers, with permanent medical assistance, a therapeutic education (TE) at each visit and systematic control of understanding and rigor. It's a rigorous approach that requires a high degree of commitment from clinicians, patients and their families (2). The results of this analysis suggest that the daily consumption of small amounts of multiple allergens daily (even in those with asthma, eczema or those at high risk of atopy) may be safe and effective.

In 2019, according to Cincinnati research in the open-label phase of the MFOIT study (n = 70, age 5– 22 years), participants received omalizumab (weeks 1–16) and multi-OIT (2–5 allergens; 1 g each; weeks 8–30), after which they were tested by food challenge (week 30). Subsequently, 60 eligible participants (excluding 10 dropouts) were randomized 1:1:1 in a blinded manner to receive either 0 mg, 300 mg, or 1 g of food allergens (weeks 30–36). These participants were then tested again by food challenge at week 36. Success was defined as passing the 2 g food challenge to at least 2 foods at week 36. Most participants were able to reach a dose of 2 g or more of each of 2, 3, 4, and 5 food allergens (as applicable to the participant's food allergens in OIT) in the week 36 food challenges. The authors found no evidence that a 300 mg dose differed from a 1 g dose in maintaining desensitization, and both together were more effective than OIT discontinuation (0 mg dose) (85% vs 55%, P = 0.03). Fifty-five percent of the intent-to-treat participants and 69% of the per-protocol participants randomized to the 0 mg arm showed no objective reactivity after 6 weeks of discontinuation. Cross-desensitization was observed between cashew/pistachio and walnut/pecan when only one of the foods was part of the OIT. There were no statistically significant safety differences between the three arms. These results demonstrate for the first time that omalizumab-facilitated MF-OIT and induces changes in immune polarization. Multi-OIT promoted a decrease in Th2A and Th17 cell frequencies while increasing regulatory markers in blood, particularly evidenced for patients aged 10 and over for whom desensitization was successful. Such results will need to be confirmed with a larger cohort of patients in double-blind, placebo-controlled clinical trials, the limitations of this study are due to the small number of participants (19).

Discussion

Current guidelines for OIT emphasize the importance of accurate diagnosis and shared decision making before initiating the protocol, as it is a logistically demanding, time-consuming and risky therapy.

Therefore, allergists, patients and their families need to be aware of and consider all aspects of this process. The primary goal of OIT is not to cure FA, but rather to increase tolerance to the allergen, improve quality of life, reduce the risk of serious reactions in the event of accidental ingestion, and reduce the psychological distress and anxiety associated with the disease.

The evidence is still limited and there is little data on long-term tolerance. There is a need for studies in this area to provide good quality evidence for standardized protocols. At present, many allergists (especially in France) have adopted protocols based on ongoing clinical research trials, with protocol initiation in specialized centers and cautious dose escalation at home to acquire small maintenance doses. Obviously, the optimal age range is between 4 and 7 years. Exclusion factors include patients with partially controlled allergic comorbidities, immune disorders, and neoplasia. It is important to be aware of the social context and to give priority to motivated and rigorous families.

Risks associated with OIT include SARs occurring at home, after the dose has been taken and, in the long term, severe anaphylaxis due to tolerance breakdown (after irregular or spaced dosing) or eosinophilic esophagitis. Targeted patient selection, close follow-up, telephone/email hotlines and TE sessions are essential to reduce the incidence of SAR's. Efficacy and risks must be discussed transparently with patients and their families, as written in informed consent forms and patient OIT protocols. Detailed information on the need for daily intake, dose adjustment in the context of cofactors or reactions, and rapid feedback of ARs are required. A higher frequency of ARs may be associated with specific predictors such as comorbidities (partially controlled atopic dermatitis, rhinitis, asthma), high skin test and IgE levels (20, 21). Indicators of OIT failure reported in several studies are high maintenance dose, high IgE level and low CRD on OFC. Low maintenance doses and, most importantly, matching the dose to the severity of the phenotype are considered the correct approach (4, 5, 20).

Low-dose maintenance therapy, multi-food if polyallergic, with slow dose escalation and tailored to the patient, therefore appears to be a safe and effective approach for children at risk of anaphylaxis. According to the studies cited, small doses have the same effect on efficacy as large maintenance doses, with a better safety profile and lower discontinuation rates. In this sense, in our opinion, the idea of starting MFOIT based on an accumulation of elements with a high predictive value in a child who has already experienced anaphylaxis and/or polyallergy remains an option of medical and ethical interest to be studied and proposed to the family. Although data are scarce, available analyses of quality of life suggest an improvement over time in most studies (20, 21).

Conclusion

OIT remains a promising therapy, reserved for specialized centers. It seems important to be able to offer it early, before teen aging or even as early as pre-school age. A review of the various studies shows the importance of identifying severe phenotypes at risk of SARs and of individualizing a closely supervised MFOIT, aiming at a slow induction phase (preferably without rush), the administration of low maintenance doses or even co-treatments for maintenance periods adapted to the phenotype of allergy severity and family possibilities.

Many questions still need to be answered: to identify the clinical characteristics and biomarkers of SARs and efficacy, and to guide the protocol in terms of optimal duration, testing these therapies in other populations (i.e., ethnic and racial groups that were underrepresented in these trials) and in patients with multiple comorbidities will also be useful. Current trials are significant for the pediatric age group, but extending research to the adult population remains another major challenge. Finally, specific tools will need to be developed to assess the impact on quality of life. This still requires larger, real-life clinical studies.

Conflict of interest

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

REFERENCES

1. Otani IM, Bégin P, Kearney C, Dominguez TL, Mehrotra A, Bacal LR, et al. Multiple-allergen oral immunotherapy improves quality of life in caregivers of food-allergic pediatric subjects. Allergy Asthma Clin Immunol. 2014;10(1):25.
2. Jones SM, Kim EH, Nadeau KC, Nowak-Wegrzyn A, Wood RA, Sampson HA, et al. Efficacy and safety of oral immunotherapy in children aged 1-3 years with peanut allergy (the Immune Tolerance Network IMPACT trial): a randomised placebo-controlled study. Lancet. 2022;399(10322):359-71.
3. Vickery BP, Berglund JP, Burk CM, Fine JP, Kim EH, Kim JI, et al. Early oral immunotherapy in peanut-allergic preschool children is safe and highly effective. J Allergy Clin Immunol. 2017;139(1):173-81.e8.
4. Grzeskowiak LE, Tao B, Knight E, Cohen-Woods S, Chataway T. Adverse events associated with peanut oral immunotherapy in children - a systematic review and meta-analysis. Sci Rep. 2020;10(1):659.
5. Patrawala M, Shih J, Lee G, Vickery B. Peanut Oral Immunotherapy: a Current Perspective. Curr Allergy Asthma Rep. 2020;20(5):14.
6. Sugiura S, Kitamura K, Makino A, Matsui T, Furuta T, Takasato Y, et al. Slow low-dose oral immunotherapy: Threshold and immunological change. Allergol Int. 2020;69(4):601-9.
7. Barshow SM, Kulis MD, Burks AW, Kim EH. Mechanisms of oral immunotherapy. Clinical & Experimental Allergy. 2021;51(4):527-35.
8. Nguyen K, Lewis MO, Hanna E, Alfaro MKC, Corrigan K, Buonanno J, et al. Safety of Multifood Oral Immunotherapy in Children Aged 1 to 18 Years at an Academic Pediatric Clinic. J Allergy Clin Immunol Pract. 2023;11(6):1907-13.e1.
9. Kulis M, Yue X, Guo R, Zhang H, Orgel K, Ye P, et al. High- and low-dose oral immunotherapy similarly suppress pro-allergic cytokines and basophil activation in young children. Clin Exp Allergy. 2019;49(2):180-9.
10. Vickery BP, Vereda A, Casale TB, Beyer K, du Toit G, Hourihane JO, et al. AR101 Oral Immunotherapy for Peanut Allergy. N Engl J Med. 2018;379(21):1991-2001.
11. Blumchen K, Trendelenburg V, Ahrens F, Gruebl A, Hamelmann E, Hansen G, et al. Efficacy, Safety, and Quality of Life in a Multicenter, Randomized, Placebo-Controlled Trial of Low-Dose Peanut Oral Immunotherapy in Children with Peanut Allergy. J Allergy Clin Immunol Pract. 2019;7(2):479-91.e10.
12. Soller L, Abrams EM, Carr S, Kapur S, Rex GA, Leo S, et al. First Real-World Safety Analysis of Preschool Peanut Oral Immunotherapy. J Allergy Clin Immunol Pract. 2019;7(8):2759-67.e5.
13. Moraly T, Pelletier de Chambure D, Verdun S, Preda C, Seynave M, Vilain AC, et al. Oral Immunotherapy for Hazelnut Allergy: A Single-Center Retrospective Study on 100 Patients. J Allergy Clin Immunol Pract. 2020;8(2):704-9.e4.
14. Giannetti A, Ruggi A, Ricci G, Giannì G, Caffarelli C. Natural History of Hazelnut Allergy and Current Approach to Its Diagnosis and Treatment. Children (Basel). 2023;10(3).
15. Elizur A, Appel MY, Nachshon L, Levy MB, Epstein-Rigbi N, Pontoppidan B, et al. Walnut oral immunotherapy for desensitisation of walnut and additional tree nut allergies (Nut CRACKER): a single-centre, prospective cohort study. Lancet Child Adolesc Health. 2019;3(5):312-21.
16. Yanagida N, Okada Y, Sato S, Ebisawa M. New approach for food allergy management using low-dose oral food challenges and low-dose oral immunotherapies. Allergol Int. 2016;65(2):135-40.
17. Bégin P, Winterroth LC, Dominguez T, Wilson SP, Bacal L, Mehrotra A, et al. Safety and feasibility of oral immunotherapy to multiple allergens for food allergy. Allergy Asthma Clin Immunol. 2014;10(1):1.
18. Eapen AA, Lavery WJ, Siddiqui JS, Lierl MB. Oral immunotherapy for multiple foods in a pediatric allergy clinic setting. Ann Allergy Asthma Immunol. 2019;123(6):573-81.e3.
19. Andorf S, Purington N, Kumar D, Long A, O'Laughlin KL, Sicherer S, et al. A Phase 2 Randomized Controlled Multisite Study Using Omalizumab-facilitated Rapid Desensitization to Test Continued vs Discontinued Dosing in Multifood Allergic Individuals. EClinicalMedicine. 2019;7:27-38.
20. de Silva D, Rodríguez Del Río P, de Jong NW, Khaleva E, Singh C, Nowak-Wegrzyn A, et al. Allergen immunotherapy and/or biologicals for IgE-mediated food allergy: A systematic review and meta-analysis. Allergy. 2022;77(6):1852-62.
21. Howe LC, Leibowitz KA, Perry MA, Bitler JM, Block W, Kaptchuk TJ, et al. Changing Patient Mindsets about Non-Life-Threatening Symptoms During Oral Immunotherapy: A Randomized Clinical Trial. J Allergy Clin Immunol Pract. 2019;7(5):1550-9.