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Oral immunotherapy for food allergy: Translation from studies to clinical practice?

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ABSTRACT

Oral immunotherapy (OIT) is now recognized as an alternative active treatment to strict food avoidance in certain patients with IgE-mediated food allergy. Studies have confirmed the efficacy of OIT to desensitize children with allergy to cow's milk, eggs, and peanuts. The benefits, risks, and constraints of OIT are becoming increasingly well understood. However, there is no consensual criteria to select patients to whom OIT could be proposed, and many issues remain to address including the definitions of desensitization and long-term efficacy, the assessment of patient's experience in real life, the optimization of buildup and maintenance protocols, and the utility of multiple food OIT. The recent authorization by medical agency concerning the first medicine for peanut OIT is a step forward towards higher standardization in the practice of OIT. This article summarizes in comprehensive narrative format data on efficacy, tolerance, impact on quality of life and adverse effects of OIT and discuss elements to consider in clinical practice before starting OIT.

Keywords: Oral immunotherapy, Food, Allergy, Desensitization, Anaphylaxis, Shared decision.

THE NEED FOR ALTERNATIVES TO FOOD AVOIDANCE FOR CERTAIN PATIENTS

IgE-mediated food allergies (FAs) are common and affect 4–8% of children and 3–4% of adults.[1] Spontaneous recovery occurs in 60–80% of cases for school age children with an IgE-mediated allergy to cow's milk (CM) or eggs[2] and in 10–20% of cases for children with peanut or tree-nut allergies.[3] FAs are the leading cause of anaphylaxis of children in Europe.[4] Anaphylactic reactions to food, sometimes severe, are becoming increasingly frequent.[5,6] A study of 32 pediatric centers in France reported that 166 children were hospitalized in pediatric intensive care for anaphylaxis between 2003 and 2013 and that food allergies (mainly milk and peanut allergies) represented 37% of admissions.[7] Food anaphylaxis is sometimes fatal. In France, the Allergy-Vigilance® network (AVN) reported 5 deaths among the 105 children who presented with food anaphylaxis at school between 2005 and 2018.[8,9] The risk of accidental ingestion once the diagnosis of an IgE-mediated FA has been made is difficult to transpose from one country to another. In North America, the annual incidence rate of accidental peanut exposure for allergic children is 12.4–23.5%.[10,11] In Japan, accidental exposure occurs in 41.9% of allergic children, which varies according to age (17–36% for CM, 19.2–49.6% for eggs).[12]

Conventional management of FAs is based on food avoidance, education, carrying an appropriate emergency kit, and the treatment of allergic reactions that occur in the event of accidental exposure.[13] However, such treatment is not suitable for

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certain patients and their families.[14] Elimination diets are difficult to follow and can be frustrating, especially for commonly consumed foods (CM, eggs, peanut, nuts). They can be a source of food neophobia, cause nutritional deficiencies, lead to anxiety, and reduce quality of life (QoL).[15] Food labeling for notifiable allergens is sometimes complex, difficult to interpret. The vigilance necessary when eating meals, particularly outside the home, and the fear of allergic reactions through accidental exposure are sources of an impaired QoL and stress or anxiety and can affect social relations.[15]

The development of therapeutic alternatives to prevent allergic reactions, particularly the most severe ones, has been identified as a priority by allergic patients and professionals involved in the management of FAs.[15,16] In this context, research on oral immunotherapy (OIT), in particular, for peanut, has recently undergone accelerated development, and OIT is now increasingly used, with very heterogeneous practices.[17] OIT has mainly been studied for allergies to CM, eggs, and then peanut in native foods, powders, flour, and commercial products in the absence of standardized products or drugs. The results of the first phase III randomized placebo-controlled trial using a drug containing standardized amounts of peanut protein (AR101, Palforzia®, Aimmune Therpeutics, Brisbane, Calif) were published in 2018.[18] The marketing authorizations granted by the health authorities to Palforzia® for peanut OIT for children marks a turning point and the beginning of the standardization of the practice of OIT.

OBJECTIVE

This article reviews in comprehensive narrative format the main points of interest regarding OIT guidelines for IgE-mediated food allergies, OIT efficacy and tolerance, impact of OIT on QoL, and risks and constraints of OIT.

METHODS

This narrative review was designed to assess the latest data on OIT for IgE-mediated food allergies. We searched the United States National Institute for Biotechnology Information/National Institutes of Health/National Library of Medicine PubMed database (https://www.ncbi.nlm.nih.gov/pubmed) for studies pertaining to OIT, guidelines, efficacy, tolerance, and risks for food allergies in the following main keyword/topic areas: OIT, food allergies including peanut allergy, anaphylaxis, efficacy, tolerance, adverse effects, comorbidities, quality of life.

The searches for each topic area, search terms used for each, and main results of each search were limited to data published within a 10-year time frame.

OIT IN GUIDELINES FOR IGE-MEDIATED FOOD ALLERGIES

Recommendations concerning the practice of OIT for IgE-mediated FAs have been proposed in different countries[12,19-22] (Table 1). OIT is generally positioned as an effective option for inducing desensitization (DS), ie, increasing the threshold of reactivity to the allergen during treatment.[12,20,22] The objective is to prevent the occurrence of allergic reactions or reduce their severity in the event of accidental exposure.[12,20,22] However, there is no standardized definition of DS.[14] OIT can also induce longer tolerance to the allergen with 2 different endpoints, "sustained unresponsiveness" (SU) and oral tolerance. SU is now largely defined as the lack of clinical reaction to a food allergen after active therapy has been discontinued but with some level of continued allergen exposure required to maintain the SU state, whereas oral tolerance describes a complete lack of reactivity without the need for continued allergen exposure. However, the data are still too limited, heterogeneous and most studies report SU outcomes but not tolerance.[20,22] The guidelines do not describe specific criteria for selecting patients to whom OIT should be offered. The notion of FA severity appears to be inadequate to determine eligibility for OIT because the risk of reactions and their severity are not predictable and do not correlate with the psychosocial impact of FAs on patients and their families.[22] Recommendations emphasize on the importance of a shared decision with the patient and his/her family before initiating and during OIT.[21,22] OIT is seen as a personalized treatment, adapted to the patient's context,

Recommendations	Country	Main points of interest of the recommendations
Martorell et al. Oral immunotherapy for food allergy: a Spanish guideline. Immunotherapy egg and milk Spanish guide. (2017)[19]	Spain	Focus on cow's milk and egg OIT. Determination of the eligibility criteria for starting OIT for these 2 foods (after 2 years of age for cow's milk and after 5 years of for eggs) and contraindications. Determination of the prerequisites and safety conditions for implementation of the OIT. Determination of useable consumer products and practical ways of implementing OIT.
Pajno et al. Clinical practice recommendations for allergen-specific immunotherapy in children: the Italian consensus report (2017)[20]	Italy	Practice of OIT in expert centers in allergology. The criteria for selecting patients, children/adults, who can benefit from OIT are not known. Foods to consider for OIT: cow's milk, eggs, and peanut.
Ebisawa et al. Japanese guidelines for food allergy (2020)[12]	Japan	Guidelines for food allergies, with a sub-chapter on OIT. Update of definitions, clinical forms, and diagnoses in terms of food allergies. OIT is indicated for any patient with an IgE-mediated food allergy proven by an oral food challenge whose clinical course is not that of naturally resolving.
Pajno et al. EAACI Guidelines on allergen immunotherapy: IgE-mediated food allergy (2020)[21]	Europe	OIT is a therapeutic option for inducing DS in children from 4 to 5 years of age with an IgE-mediated food allergy for cow's milk, eggs, and peanut. During the escalation phase, dose increases to be carried out under medical supervision in a structure capable of treating allergic emergencies. Need for informed consent before the initiation of OIT. Contraindications and unresolved points identified.
Begin et al. CSACI guidelines for the ethical, evidence-based and patient-oriented clinical practice of oral immunotherapy in IgE-mediated food allergy (2020)[22]	Canada	Recommendations for a patient-centered practical approach, analyzing 22 criteria divided into 5 domains (sociopolitical, population, clinical, organizational, economic). OIT can be offered to all patients, including adults, for all foods and also in the event of multiple food allergy. The notion of the severity of the initial reaction should not be taken into account to contraindicate OIT. Uncontrolled asthma is an absolute contraindication to starting OIT. During the escalation phase, dose increases to be carried out under medical supervision in a structure capable of treating allergic emergencies, with 1 h of monitoring. OIT can be carried out with various products, including those for industrial consumption. Need for informed consent before initiation of OIT.

Table 1. Main points of interest from learned society recommendations on oral immunotherapy (OIT) for IgE-mediated food allergies (FAs)

considering his/her wishes and objectives, eating habits, experience, and motivation.[14,15,21-23] It involves constraints and risks, requires commitment and strong compliance, and is currently envisaged for an "indefinite" period.[14,23] Recommendations specify that centers practicing OIT must have expertise in this type of care and have infrastructure that allows the regular and personalized follow-up of patients, the performance of oral food challenges (OFCs), and the management of anaphylactic reactions.[12,21,23,24] They also recommend performing each dose increase in centers under medical supervision.[21,22] However, studies have reported the efficacy and safety of reintroduction procedure performed at home for CM or hen's egg allergy for instance and the Cochrane meta-analysis confirmed that many OIT protocols were carried out both in hospital or at home.[25,26] A signature of consent specifying the benefits, risks, and methods of OIT is customary.[12,21,22,24] The recommendations also agree on the contraindications of OIT, in particular, uncontrolled asthma, eosinophilic esophagitis, pregnancy, and active neoplasia.

They specify that OIT can be performed with fresh or store-bought food.[21,22] However, the amount of allergen in manufactured products can vary. The products and vehicles used in studies (more-or-less processed and defatted native foods, commercial products, matrices) have been highly variable, and has led the health authorities to impose standardization of the allergenic content of products used for OIT for safety reasons.[27] Palforzia® is, to date, the only drug to have obtained marketing authorization. Although several studies suggest greater efficacy of OIT when started at preschool age,[28] the European Academy of Allergy and Clinical Immunology (EAACI) recommends waiting for a chance for the allergy to resolve naturally before starting OIT,[21] and only recommends it from the age of 4–5 years and not for adults. In Spain and Canada, OIT is recommended before this age because of its very good tolerance.[19,22] For the EAACI, only OIT for CM, eggs, and peanut is recommended and only in children.[21] In Canada, OIT is recommended for all foods in children and adults.[22]

INTERPRETATION OF STUDIES ASSESSING OIT EFFICACY

Desensitization (DS)

OIT has mainly been studied for CM, egg, and peanut allergies. The effectiveness of OIT for these foods has been well demonstrated in terms of DS, but the benefit in terms of risk reduction in the event of accidental exposure has been poorly studied.

A meta-analysis of 36 randomized controlled trials carried out on 2126 participants (mainly children) treated with OIT for FAs to CM, eggs, and peanut showed that OIT induces DS in 68% of patients with CM and peanut allergies and 84% of egg-allergic patients.[29] Another meta-analysis of 18 randomized controlled trials (8 versus placebo) and 5 non-randomized studies involving almost 1000 patients with CM, egg, or peanut allergies showed that 76.9% of patients treated by OIT were desensitized, versus 8.1% of control subjects, with a benefit in children not found in adults.[30] In a Cochrane meta-analysis of 10 controlled trials (3 versus placebo) evaluating egg-based OIT on 249 children, DS was induced in 82% of children treated by OIT (consumption of 1–7.5 g of egg protein) and 10% of controls.[26] A Cochrane meta-analysis showed that OIT for CM allergy allowed DS (consumption of 150–243 ml of milk) in 62% of the 106 children treated with OIT versus 8% of the 90 control subjects, with strong heterogeneity of the 5 randomized trials analyzed.[31] In a meta-analysis of 9 randomized controlled trials evaluating the efficacy of peanut OIT for a median duration of 1 year on 917 participants, the relative risk of not having a reaction during an OFC with peanut was 12.42, in favor of OIT.[32]

There are few studies regarding OIT in adults. Mäntylä et al. reported the results in 10 adult patients with milk OIT, 9 adult patients with peanut OIT, and 4 adult patients with egg OIT.[33] The median dose of milk protein increased by 60-fold during OIT compared to the allergen challenge dose. In peanut OIT the median dose increased by eight-fold and in egg allergy the dose increased with OIT by 35-fold. The authors concluded that OIT can be given in adult

patients with severe milk, peanut, or egg allergy only in selected cases, leading to DS even if it is not clear whether persistent tolerance can be achieved.[33]

The interpretation of these results must consider natural resolution of the allergy, which occurs more frequently for CM and egg allergies than peanut allergies, and both the adverse effects and constraints of OIT. Moreover, in the absence of a consensus, there is considerable variability in the diagnostic criteria for DS, the maintenance target doses, the degree of cooking for CM and eggs, and the duration of the escalation and maintenance phases.[14,27] The maintenance doses used ranged from 190 to 8000 mg of egg protein, 500 to 8250 mg of CM, and 125 to 4000 mg of peanut protein[27,34]. Modeling has shown that increasing the reactogenic dose of peanut protein to 300 mg or more, regardless of the initial reactogenic dose, reduces the risk of reaction by more than 95% in the event of accidental exposure.[35] This dose, corresponding to approximately 1 peanut, was chosen as a maintenance dose for studies using Palforzia®.[19,36] Such models do not exist for OIT for other foods. The follow-up of children treated by OIT indicates that extending the duration of the maintenance phase would increase the effectiveness of DS. Among children treated with Palforzia®, 48.1% of those treated for 1.5 years and 80.8% of those treated for 2 years tolerated the cumulative dose of 4043 mg of peanut protein during an OFC.[37] Similarly, in a study comparing egg OIT in 40 children to placebo, 22% of children treated by OIT for 10 months tolerated a cumulative dose of 4 g of raw egg white protein during an OFC, versus none in the placebo group; 12 months later, 75% of children treated by OIT tolerated the 8-g protein dose.[38]

More recent studies have confirmed the effectiveness of OIT for other foods. In the CRACKER study, which evaluated the efficacy of OIT for walnut (maintenance dose: 1200 mg protein) in 55 children aged 7.9 years, 49 children (89%) were desensitized, ie, tolerated at least 4000 mg of protein during an OFC.[39] In this study, 46 patients were also allergic to pecan nuts and 15 to cashew nuts. Walnut OIT induced pecan DS in all pecan-allergic children and in 14 of 15 cashew-allergic patients.

In a study evaluating cashew OIT (maintenance dose: 4000 mg protein, approximately 16 cashew nuts) in 50 eight-year-old children, OIT induced DS (tolerance of 4000 mg protein during an OFC) in 44 children (88%).[40] Cashew OIT also induced pistachio DS in all pistachio-allergic children.

In a double-blind, multicenter trial evaluating wheat OIT (target maintenance dose: 1445 mg protein) in 23 children (mean age: 8.7 years) versus placebo (n = 23), OIT induced DS (tolerance of at least 4443 mg protein during an OFC) at 12 months in 52.2% of children treated with OIT and none of the children in the placebo group.[41]

A study also showed that sesame OIT induced DS (tolerance of 4000 mg of protein or 17 g of sesame puree) in more than 88% of cases.[42]

Tolerance and sustained unresponsiveness

Tolerance and sustained unresponsiveness have been less studied than DS. The most frequently chosen endpoint to assess tolerance is the absence of a reaction during an OFC using high doses of allergens, after a short period of discontinuation of OIT (approximately 2 weeks–3 months).[34] A meta-analysis of 7 randomized trials of OIT for CM, egg, or peanut allergies showed that OIT could induce tolerance in 31.8% of treated patients and 11.1% of control subjects.[30] In the Cochrane meta-analysis evaluating OIT with egg, 45% of patients treated by OIT and 10% of control subjects could ingest a quantity of eggs normal for their age after stopping OIT.[26] In the IMPACT study, which evaluated early peanut OIT in children aged 12–48 months, DS (absence of a reaction during an OFC with 5000 mg of protein) was induced in 71% of children after 134 weeks of OIT and tolerance, assessed 26 weeks after the discontinuation of OIT, was maintained in only 21% of them.[28] In this study, early OIT was associated with more frequent acquisition of tolerance.[28] In a study on OIT for egg allergy, 75% of children treated for 22 months by OIT tolerated a dose of 8 g of protein during an OFC and 28% tolerated this dose 2 months after stopping OIT.[38]

The POISED study evaluated the effect of stopping OIT after 2 years of peanut OIT (maintenance dose: 4000 mg protein) or continuing it with lower daily doses (300 mg).[43] While 85% of children

tolerated 4000 mg of protein after 2 years of OIT, 13% of those who stopped all peanut-protein consumption and 37% of those consuming 300 mg of protein daily still tolerated 4000 mg of protein 1 year later. However, this dose, corresponding to approximately 13–15 peanuts, is high, and 74% of children who continued OIT by the daily ingestion of 300 mg of protein per day (26% of those who stopped all peanut consumption) tolerated 900 mg of protein or more, suggesting that they were protected against accidental consumption of small amounts of peanut-containing products.

These results indicate that once DS has been obtained, reactivity to the allergen rapidly increases again for most patients in the absence of its regular consumption, suggesting that most patients who have started OIT should continue it for an indefinite period. The optimal duration of the maintenance phase and the daily dose of allergen to be ingested have not yet been established. Continuous consumption of the allergen at least 3 to 4 times per week is often recommended and adjusted according to the patient's objectives (protection in the event of accidental exposure, consumption of small quantities) and their ability to continue treatment.[23] A real-life study showed that the daily consumption of moderate doses of peanut protein (1200 mg, approximately 4 peanuts) after obtaining DS is associated with better compliance than the consumption of higher doses (3000 mg of protein/day).[44] Similarly, the DEVIL study, which compared the efficacy of high doses of peanut OIT (3000 mg of protein per day) with lower doses (300 mg per day) in young children (median age: 28.5 months) showed that the risks of adverse events and study withdrawal were higher in the high-dose group.[45] These results suggest that ingesting lower maintenance doses may be preferable in the long term.

Most studies have focused on single-allergen OIT. Few studies have evaluated the efficacy and tolerance of OIT for mixtures of food allergens.[46,47] The interest would be to be able to carry out OIT on multiple food allergic patients, in particular, those with an allergy to peanut and/or tree nuts, considering the interest of starting early in life and, in particular, the constraints associated with the implementation of OIT in a hospital environment. In a retrospective study of patients performing peanut OIT (n = 162) or multi-allergen OIT (2–4 allergens, n = 77), the time to reach the maintenance phase was comparable between patients receiving OIT for the allergen mix and those receiving OIT for peanut alone (231 versus 245 days).[47] Furthermore, the efficacy appeared to be comparable, as 80% of patients receiving multi-allergen OIT and 85% receiving peanut OIT reached the maintenance phase. The tolerance of multi-allergen OIT also appeared to be good in terms of the number of cases of anaphylaxis under OIT: after 1 year, adrenaline was used by 13% of patients in the peanut OIT group versus 8% of patients in the multi-allergen OIT group.

Impact of OIT on quality of life

OIT studies have taken little account of the psychosocial dimension of FAs, the deterioration of long-term QoL and, more generally, the patient's expectations.[15,26–30] A number of questionnaires, such as the FAQLQ, have been validated to assess the QoL of patients on an elimination diet, but only partially reflect the experience of OIT.[15] Although many randomized controlled or real-life studies have shown an improvement in QoL scores of children and their families after OIT, a meta-analysis of randomized controlled studies comparing short-term (1 year) QoL scores, with or without OIT for peanut allergy, did not show a benefit of OIT.[34,48,49] A study of 191 children aged 4–12 years treated by OIT for allergies to CM, egg, peanut, sesame seeds, or tree nuts, showed that the QoL perceived by the parents and evaluated by the FAQLQ-PF questionnaire, improved between the start of the OIT and the maintenance phase in several dimensions, whereas the score was stable for the control subjects. Factors associated with improvement were having a single FA, younger age at the onset of OIT, and a worse initial score.[50] Another study involving 57 children treated by peanut OIT and 20 control subjects treated by avoidance for 2 years showed an improvement in the QoL assessed by the PQLI questionnaire for the parents of children in the OIT group only, with no improvement for the children.[51] These data suggest that parents may overestimate the impact of OIT on their children's QoL. Patients less affected by their FA at the start of treatment

may perceive a deterioration in their QoL at the start of treatment[23] associated with the adverse effects of the escalation phase (stomach pain, aversion, OIT constraints, induced allergic reactions, use of adrenaline), medical follow-up, and anxiety induced by the protocols before this improves over the course of treatment, especially when the DS objectives are attained.[37]

Risks of OIT

Virtually all patients on OIT experience mild to moderate treatment-related adverse effects.[52] Meta-analyses show that local (oropharyngeal, gastrointestinal symptoms, perioral rash) and systemic reactions are more frequent for patients on OIT than those who are not.[30] In the Cochrane meta-analysis evaluating egg-based OIT in 249 children, 21 (8.4%) of the children on OIT had used adrenaline versus none of the control subjects.[26] The meta-analysis of 9 randomized controlled trials evaluating the efficacy of short-term peanut OIT (median duration 1 year) in nearly 900 participants showed that patients on OIT had more occurrences of anaphylaxis (RR = 3.12), and used adrenaline more frequently (RR = 2.21) than control subjects.[32]

In studies of Palforzia®, which included 944 children with a median age of 9 years treated for a short period (median 49 weeks), 829 (87.8%) experienced treatment-related adverse effects.[53] Their frequency was 243 events per patient year during the first 2 days of the escalation phase, 58.7 during the escalation phase, and then decrease from 21.7 at the start of the maintenance phase to 2 between weeks 79 and 91 of maintenance. Adverse effects were considered to be mild in 52.6% of cases and moderate in 35.2%; 24 children experienced severe adverse effects, reported as anaphylaxis for 10.[53] Adverse effects, mainly oropharyngeal pruritus and digestive symptoms, occurred in the majority of cases at the beginning of the escalation phase before reaching the dose of 80 mg of protein. They occurred 4–8 min after intake and lasted 15–30 min. In total, 110 participants (11.7%) stopped OIT due to adverse effects.[53] In a retrospective study evaluating peanut OIT in 270 patients aged 4–18 years, anaphylaxis was reported for 63 (23.3%) patients and isolated gastrointestinal symptoms for 110 (40.7%).[54] Clinicians should also keep in mind that OFC during OIT procedure may be at risk of refractory/near fatal/fatal anaphylaxis, even if very rare. Two deaths during OFC have been reported before: a death in a 11-year-old child undergoing a peanut OFC prior to beginning an OIT and a death in a 3-year-old child during an OFC with baked cow's milk.[55,56]

The risk of anaphylaxis appears to be higher for OIT for CM: a study that evaluated 1100 cases of OIT to various foods (milk, egg, peanut, sesame seeds, nuts) showed that allergic reactions requiring adrenaline in healthcare settings and at home were more frequent for OIT with CM allergy than for OIT with other foods (26.8% versus 11.3% and 13.8% versus 5.8%, respectively).[42] A retrospective cohort study among 342 children with persistent CM allergy undergoing OIT over a 20-year period assessed the risk of severe anaphylaxis during and after stopping OIT.[57] During OIT, 12 children (3.5%) presented severe anaphylactic reactions that needed an adrenaline injection. Among the 96 children who stopped OIT, 6.3% experienced a severe reaction induced by accidental ingestion of milk with 2 fatal outcomes. Further studies are needed to confirm these data but a new approach using biologics may be considered in patients who may be at very high risk of severe anaphylaxis by stopping OIT.

However, unlike the reactions that occur in real life, the adverse reactions under OIT occur within the framework of taking the treatment, in informed patients, under medical or parental supervision. A retrospective study suggested that the risk of occurrence of adverse effects during OIT for CM and egg allergies could be reduced by the use of information documents and written action plans specifying that it is preferable to avoid taking doses of OIT on an empty stomach or going to bed or playing sports within 2 h of ingestion and to reduce the dose in the event of infection, asthma attack, menstruation, or bowel disease.[58]

In addition, a randomized controlled study involving 50 children treated by peanut OIT suggests that considering mild local reactions as reflecting the acquisition of DS rather than as an adverse effect would reduce the risk of occurrence of adverse effects and improve compliance and

the patient experience.[59] These results show the importance of information and follow-up and of the availability of the medical team setting up the OIT with these patients. Standardization of the information necessary during OIT intended for the child, his/her family, and his/her relatives, at the national level, is necessary.

The follow-up of adverse effects linked to OIT should also search for eosinophilic esophagitis (EO). Its occurrence is estimated to be between 0.5 and 5% in OIT.[60–62] The diagnosis is however complicated by the fact that the gastrointestinal adverse effects related to OIT are frequent and subjective. Some patients have pathological criteria in favor of EO on digestive biopsies without symptoms suggestive of the disease.[63] In young children, food refusal, abdominal pain, and recurrent nausea and vomiting may be warning signs of EO, whereas in older children or adolescents, dysphagia is the most suggestive symptom. In cases of suspicion of EO, the diagnosis is confirmed by carrying out a digestive endoscopy with esophageal biopsies. The care of these patients is based on a specialized multidisciplinary approach that currently lacks consensus.

Immunotherapy and adjuvant therapies

Omalizumab and etokinmab are being studied as an adjuvant treatment during OIT protocols to reduce the risk of severe reactions.[64] In CM, egg, and peanut OIT, omalizumab could reduce the number and severity of reactions during the escalation phase and allow the maintenance phase to be attained more quickly.[65–68] However, the use of omalizumab in combination with OIT would not increase the proportion of patients reaching the maintenance phase.[64] Dupilumab, an anti-IL4 receptor antibody, is currently being studied in combination with OIT for milk or AR101 (peanut OIT).[69,70] However, the effects on efficacy and safety of dose adjustment, according to body weight and total IgE levels, or in fixed doses are uncertain. Hence, the duration, dosage, and effectiveness of omalizumab treatment in OIT remains to be clarified. The GA2LEN Task Force made no recommendation for or against offering biologicals for treating food allergy given the very low certainty of evidence.[71]

The data concerning the tolerance of OIT and the risk of serious reactions encourage the development of other drugs. EPIT (epicutaneous immunotherapy) for peanut allergy would make it possible to induce DS by the transcutaneous route, in particular in the youngest, by applying a patch containing very small quantities of allergen (250 µg of peanut protein), limiting the risk of adverse effects.[72,73] In the GA2LEN guidelines for immunotherapy, the task force recognizes that EPIT in children aged 4–11 years probably results in an increase in the threshold at which they react to peanut whilst on therapy.[71] The task force felt it was important to highlight the positive evidence in trials to date despite EPIT is not currently available or licensed. Other drugs are in development including modified proteins with less allergenicity, probiotics and DNA vaccines.[74] A specific probiotic supplementation has been proposed as adjuvant treatment for OIT in peanut-allergic children (Lactobacillus rhamnosus GG ATCC 53103) and in cow's milk allergic infants (Bifidobacterium bifidum TMC3115) with improved safety outcomes.[75,76] The relationship between the microbiome and the immune system is still not well understood and further research is needed.[77].

Unmet needs and perspectives (Table 2)

Although the benefits, risks, and constraints of OIT are well described, many elements are yet to be clarified: the definition of DS, evaluation of the impact of OIT on the patient, development of biomarkers of efficacy, description of the "good responder" or "at risk" phenotypes and endotypes, age at onset according to foods, modality of the escalation and maintenance phases, optimal dose during the maintenance phase, optimal frequency and duration of long-term administration, efficacy and tolerance of OIT for multiple foods.[14] There are no consensual criteria to select patients to whom OIT could be proposed. Thus, in clinical practice, the decision of starting OIT rely on several elements including the nature of FA, the presence of asthma and comorbidities and the patient's experience and expectations (Table 3).

Patient selection (better determination of phenotype/endotype) Age to initiate OIT Choice of foods for which OIT can be indicated Evaluation of the impact of OIT on adults
Impact of cofactors
Search for predictive biomarkers of success or failure of OIT
Search for optimized OIT protocols: modality of escalation and maintenance phases, definition of optimal maintenance doses, optimal frequency and duration of long-term administration Determination of threshold doses that protect against accidental exposure (depending on the context, food, child, expectations of the family, etc.) Interest of multi-allergen OIT
Relative place of the various potential routes for immunotherapy (sublingual, epicutaneous, oral)
Impact of OIT in real life (on the threshold and frequency of allergic reactions, on the quality of life, long-term impact, etc.) Medico-economic impact of these treatments
Place of strategies to reduce side effects and optimize immunotherapy in personalized medicine (biotherapies in addition to OIT or instead of OIT)

Table 2. Main unresolved elements in the practice of oral immunotherapy (OIT) for IgE-mediated food allergies

The GA2LEN task force reported gaps regarding OIT including the predictors of response to OIT (effect of using modified food allergens [eg, baked milk and egg] to improve and accelerate tolerance in IgE mediated food allergy/use of raw or cooked egg in OIT …).[71] The authors highlighted with a high priority the need for studies to assess the ability for different factors

FA	Natural evolution of FA
	Type of FA (type of allergen, single or multiple, rare or ubiquitous allergen)
Comorbidities	Presence of uncontrolled asthma
	EO, pregnancy, malignancy
Patient's experience	Impact of FA on QoL, burden of FA, experience of FA (history of anaphylaxis)
	Eating habits
	Social habits Risk of future accidental exposure to the allergen
	Ability to treat reactions
	Patient wishes, expectations, and motivation
	Expected benefits
	Acceptation of aims, risks and constraints of OIT
Shared decisions	Documented decision-making process
	Signed informed consent

Table 3. Elements to consider to help decision of starting (or not) OIT. *FA: food allergy, EO: eosinophilic oesophagitis, QoL: quality of life, OIT: oral immunotherapy*

and biomarkers to predict good response to therapy in different age groups.

CONCLUSIONS

The decision to start OIT requires expertise in allergology and should consider many factors, including the characteristics of the FA and the patient and their wishes and expectations in a shared and documented decision-making process. OIT is indicated in selected patients due to its constraints and adverse effects, and is a personalized treatment for motivated patients. OIT is effective in inducing short-term DS for CM, eggs, and peanut, and recent data suggest its efficacy for other foods and for young children. The use of new drugs will contribute to the standardization of procedures.

Abbreviations

OIT, oral immunotherapy; FA, Food allergy; CM, cow's milk; AVN, Allergy-Vigilance® Network; QoL, Quality of life; DS, desensitization; OFC, oral food challenge; EAACI, European Academy of Allergy and Clinical Immunology; RR, relative risk; EO, eosinophilic oesophagitis.

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Authorship

Dr GP and GL were involved in study design, in data interpretation. Drafting and editing of the manuscript, reviewing of this manuscript. They confirm that they have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. GP and GL met ICMJE criteria and made the final decision about where to publish these data and approved submission to this journal.

Ethics approval

Not applicable.

Authors' consent for publication

All authors provided input into the manuscript, reviewed the final draft and provided consent for publication.

Declaration of competing interest

GP declares that he has received fees for scientific work or consulting requested by Bausch & Lomb, Meda/Mylan/Viatris, Stallergenes Greer, Novartis, ALK-Abello, and AImmune Therapeutics/Nestlé.
GL declares that he has received fees for scientific work or consulting requested by Stallergenes Greer, ALK-Abello, Novartis, GSK, AImmune Therapeutics/Nestlé, and DBV Therapeutics.

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