GUIDELINES

Oral Immunotherapy for Food Allergy: A Spanish Guideline. Immunotherapy Egg and Milk Spanish Guide (ITEMS Guide). Part I: Cow Milk and Egg Oral Immunotherapy: Introduction, Methodology, Rationale, Current State, Indications, Contraindications, and Oral Immunotherapy Build-up Phase

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Abstract

Introduction: Cow milk and egg are the most frequent causes of food allergy in the first years of life. Oral immunotherapy (OIT) has been investigated as an alternative to avoidance diets. No clinical practice guidelines on the management of OIT with milk and egg are currently available.
Objectives: To develop clinical guidelines for OIT based on available scientific evidence and the opinions of experts.
Methods: A review was made of studies published between 1984 and June 2016, doctoral theses published in Spain, summaries of communications at scientific meetings (SEAIC, SEICAP, EAACI, and AAAAI), and the consensus of opinion established by a group of experts from the scientific societies SEICAP and SEAIC.
Results: Recommendations were established regarding the indications, requirements and practical aspects of the different phases of OIT, as well as special protocols for patients at high risk of adverse reactions.
Conclusions: Clinical practice guidelines based on the consensus reached between Spanish experts are presented for the management of OIT with milk and egg.

Key words: Guide. Oral immunotherapy. Desensitization. Specific oral tolerance induction. Milk allergy. Egg allergy. Omalizumab. Sublingual immunotherapy.

Resumen

Introducción: El huevo y la leche de vaca son la causa más frecuente de alergia alimentaria en los primeros años de vida. Como alternativa terapéutica a la dieta de eliminación se han investigado otras formas de tratamiento como la inmunoterapia oral (ITO). Actualmente no existen guías de práctica clínica para el manejo de la ITO con leche y huevo.
Objetivos: Elaborar una guía clínica para el tratamiento con ITO basada en la evidencia científica disponible y en la opinión de expertos.
Métodos: Revisión de estudios publicados desde el año 1984 hasta junio de 2016, tesis doctorales publicadas en España, resúmenes de comunicaciones en congresos (SEAIC, SEICAP, EAACI, AAAAI) y consenso de opinión de un grupo de expertos de las sociedades científicas SEICAP y SEAIC.
Resultados: Se establecen recomendaciones acerca de la indicación, requerimientos, aspectos prácticos del tratamiento en las diferentes fases de la ITO, y pautas especiales para pacientes de alto riesgo de reacciones adversas.
Conclusiones: Se presenta una guía con las directrices para el manejo en la práctica clínica de la ITO con leche y huevo que aúna la opinión consensuada de expertos españoles.

Palabras clave: Guía. Inmunoterapia oral. Desensibilización. Inducción de tolerancia oral específica. Alergia a leche. Alergia a huevo. Omalizumab. Inmunoterapia sublingual.

1. Introduction

Cow milk (CM) and egg are the most frequent causes of food allergy in the first years of life [1]. Two recent European studies conducted by the EuroPrevall group reported an incidence of CM allergy and egg in the first 2 years of life of 0.54% (0.57% of infants in Spain) and 0.84% (0.78% of infants in Spain), respectively [2,3]. A study carried out in the Autonomous Community of Valencia, Spain, in which diagnosis was confirmed by oral food challenge, reported an incidence of CM allergy of 0.36% in the first year of life [4].

The only currently approved treatments for food allergy are avoidance and administration of emergency medications on accidental exposure [5].

New treatment options have therefore been explored, the most widely studied being oral immunotherapy (OIT). Milk OIT and egg OIT induce changes in the immune system and favor the development of desensitization in most patients, although there is little evidence on their long-term safety and efficacy [6].

The immunological mechanisms intervening in OIT have not been fully clarified; however, this approach is known to induce a decrease in the activation and release of mediators from mast cells and basophils, with an increase in specific IgG4 titers, a decrease in specific IgE levels, the activation of specific regulatory T cells, and T_H2-mediated inhibition of response [7-10].

Adverse reactions (ARs) to OIT are frequent and can manifest in the maintenance phase. Although such reactions are generally mild, they may be more serious and require treatment with epinephrine. While sometimes associated with cofactors (eg, exercise, infections), ARs may appear unpredictably with doses that were previously well tolerated [5,11].

Desensitization is achieved in most patients, although in at least 20% of cases OIT fails because of ARs. Therefore, new therapeutic strategies, such as adjuvant therapy with anti-IgE antibodies must be developed in order to broaden the scope of application of OIT [12].

The long-term outcome and time needed to achieve permanent tolerance of the causal food are not known [5,13,14]. Furthermore, it must be taken into account that prolongation of the maintenance phase can hamper adherence [15].

These elements of uncertainty explain why OIT is currently recommended only in the research setting and not in clinical practice.

However, the fact is that CM and egg OIT have already been introduced in clinical practice and form part of the management options of many hospitals in Spain. The heterogeneity of current protocols necessitates a clear definition of the bases for regulating the requirements for application of OIT in clinical practice, with standardization and optimization of treatments and reduction of associated risks.

The present document aims to offer clinical guidelines on the use of OIT in patients with IgE-mediated allergy to CM and egg-white proteins. By incorporating the data derived from current extensive experience, the guidelines will make recommendations for OIT during the build-up phase and subsequent maintenance treatment, with the maximum safety guarantees.

The ultimate outcome is to improve clinical practice and to allow professionals managing OIT to feel that their work is endorsed by the scientific societies SEICAP and SEAIC.

2. Methodology

The guidelines were developed based on the following elements:

- A literature search and review of the following:
  - Studies and meta-analyses of milk and egg OIT published between 1984 and June 2016 and found in the PubMed database.
  - Doctoral theses on milk and egg OIT published in Spain.
  - Abstracts referring to milk and egg OIT presented between 2010 and 2014 at the meetings of the SEICAP, SEAIC, EAACI, and AAAAI.
- Consensus between Spanish researchers with experience in OIT.
- Levels of evidence and grades of recommendation of the Scottish Intercollegiate Guidelines Network (SIGN) [16].

3. Rationale. State of the Art: Indications and Contraindications

3.1. Rationale of OIT

3.1.1. Why is OIT Postulated as a Treatment Alternative?

The spontaneous short-term course of food allergy is not favorable in all individuals and in some cases tends to persist indefinitely.

The prognosis of CM and egg allergy in children is generally good. Approximately 85% of all infants with CM allergy develop tolerance by 3 years of age [17-20]. Egg allergy persists for longer, although approximately 65% of all affected patients reach tolerance by 6 years of age [21,22].

However, more recent studies suggest a tendency towards longer persistence of milk allergy (36% of patients do not tolerate milk at 12 years of age) [23] and egg allergy (32% of the patients do not tolerate egg at 16 years of age) [24].

3.1.2. Patients with milk or egg allergy have a real and nonnegligible risk of a further reaction, which may prove serious

Food allergy is the most frequent cause of anaphylaxis, particularly in children and young adults [25]. Recent meta-analyses [26,27] reveal the incidence of anaphylactic reaction to be 4.93 cases per 100 food-allergic children.

Between 1998 and 2011, an increase was recorded in admissions to Spanish hospitals due to anaphylaxis, particularly those involving children and caused by foods (mainly CM and egg) [28].

Deaths are rare, however, and the mortality rate has remained stable in recent years, with an estimated 1.8 deaths per million food-allergic patients per year.

Although deaths secondary to anaphylaxis caused by milk and egg are infrequent, the risk must not be underestimated, particularly in patients with asthma and in adolescents. Fatal anaphylaxis occurs mainly in children and young adults and can be avoided through correct preventive or therapeutic interventions.

A prospective multicenter study carried out in the United States (514 patients aged under 15 months of age who were allergic to milk or egg, 3-year follow-up) revealed reactions in 62% of the children, of whom over half experienced >1 reaction per year [29]. The annual rate for all foods was 0.81 reactions per year. Milk caused twice as many reactions as egg (42.3% vs 22%). Most reactions were caused by accidental exposure to an allergen (87.4%), and 11.4% were severe. No significant differences in this percentage were observed between milk and egg.

In a Spanish cross-sectional observational study of milk-allergic children aged between 18 months and 12 years, ARs secondary to accidental exposure were recorded in 40% of patients in the previous year, and 15% of those reactions were severe [30].

3.1.3. The psychosocial impact of food allergy

Food allergy affects different aspects of patients' lives and their environment, with a negative impact on the quality of life of both the affected individuals and their families, owing to the repercussions of the disorder in their school and family life and to the associated costs.

Apart from the importance of the physical manifestations of food allergy, the need to follow an exclusion diet intrinsically produces emotional, psychological, and social problems. Furthermore, patients who have experienced a severe reaction live in fear of a possibly fatal reaction [31-35].

Consequently, patients demand a solution to their problems that goes beyond avoidance diets and encourage allergologists and pediatricians to search for new therapies such as OIT.

3.2. Current State of OIT: Efficacy and Safety

3.2.1. Are milk and egg OIT effective?

OIT aims to achieve 2 successive outcomes in time: desensitization and the acquisition of sustained unresponsiveness.

OIT is defined as the administration of progressively increasing doses of the food causing the allergic reaction, with the aim of relieving the symptoms resulting from natural exposure, ie, the objective of OIT is to ensure desensitization and, if possible, permanent tolerance of the food.

Oral desensitization is characterized as the reversible reduction in clinical reactivity or responsiveness achieved after exposure to progressively increasing doses of a food. Oral desensitization may be lost within a few days or weeks after suspending regular intake of the food.

Sustained unresponsiveness is defined as the permanent absence of clinical reactivity to a food even if it is not consumed on a regular basis.

3.2.1.1. Efficacy of desensitization

The efficacy of desensitization is defined as the increase in the reaction threshold measured in terms of the food dose tolerated by the patient.

These guidelines consider 2 degrees of efficacy:

- Complete desensitization: when the patient is able to tolerate a dose equivalent to a full serving of the food, thus allowing it to be added to the diet without restrictions. In the case of CM and egg, complete desensitization is achieved when the patient tolerates 200 mL of CM or 1 raw or cooked egg white (depending on the treatment outcome established).
- Partial desensitization: when the patient is able to increase the threshold of tolerance of the food compared with before OIT but does not tolerate a full serving of the food, or some of the commonly consumed presentations of the causal food. Maintenance of partial desensitization would be justified in order to avoid ARs caused by the inadvertent intake of small amounts of the food and to facilitate continuation of the desensitization process after a period of time.

Desensitization may prove more effective in small children, suggesting that immune modulation would be easier to achieve if started at an early age, as has been postulated in the case of subcutaneous immunotherapy with aeroallergens. In most patients with severe clinical manifestations of anaphylaxis and high specific IgE titers, desensitization is only partial [36,37].

Meta-analyses of controlled studies conclude that OIT is effective in inducing desensitization in most patients with IgE-mediated CM and egg allergy, although the results in terms of long-term tolerance are not clear [38-40] (Level of evidence I. Grade of recommendation A).

3.2.1.2. Efficacy in acquiring sustained unresponsiveness

The ultimate aim of OIT is to achieve sustained unresponsiveness, without AR and without having to consume the food on a regular basis.

Published studies reveal a trend towards tolerance in 38%-75% of patients with CM and egg allergy undergoing OIT after a maintenance period of 1-4 years [41,42]. Recent meta-analyses demonstrated a substantial benefit of OIT in terms of desensitization (risk ratio [RR], 0.16; 95%CI, 0.10-0.26) and suggested, but did not confirm, sustained unresponsiveness (RR, 0.29; 95%CI, 0.08-1.13) [43].

The factors that influence the acquisition of tolerance are not known, but may involve the time elapsed from complete desensitization, the doses administered during the maintenance phase, the degree of sensitization to the causal food, and other patient-related factors inherent, such as adherence to therapy. Similarly, it is not clear whether sustained unresponsiveness can be achieved in all allergic patients, provided OIT is maintained long enough, or whether some patients will never be able to achieve permanent tolerance.

Thus, OIT has been shown to be effective in achieving desensitization in patients with CM and egg allergy (Level of evidence I. Grade of recommendation A), although the maintenance period needed to secure sustained unresponsiveness is not known and it is not clear whether all patients can eventually reach tolerance.

3.2.2. Is OIT safe?

The safety of OIT is a key factor when applying the evidence gained from studies to the clinical practice setting.

Evidence on the safety of OIT has been examined in systematic reviews and meta-analyses over the last 3 years, and the conclusion is that ARs are frequent during OIT (up to 91.5% of all treated patients) [35] and in 16% of doses administered [44].

Most of the ARs reported were mild and self-limiting: itching of the mouth and lips, perioral urticaria, generalized urticaria or erythema, abdominal symptoms, rhinoconjunctivitis, mild laryngeal spasms, and mild bronchospasm [40,45]. There have also been reports of severe anaphylactic reactions [46,47], and results from controlled clinical trials show that 6.7%-30.8% of patients undergoing milk OIT and 20% of those undergoing egg OIT required epinephrine [36,37].

Eosinophilic esophagitis has been reported with OIT [48], although in no case was esophageal disease ruled out before OIT was started. A recent systematic review concluded that the combined prevalence of eosinophilic esophagitis diagnosed after OIT (milk, egg, peanut, or wheat) was 2.7% [49].

ARs may lead to patient withdrawals of 3%-20% in the case of milk OIT and 0%-36% in the case of egg OIT [50].

In conclusion, OIT is not without risks. Most of the ARs are mild, although more serious reactions are also possible.

3.3. Indications and Contraindications

3.3.1. Which patients may currently be considered candidates for milk and egg OIT?

- Patients with IgE-mediated CM and egg allergy.
- Patients who maintain clinical reactivity to CM at 2 years of age, as confirmed by oral food challenge [51] (Level of evidence II. Grade of recommendation B)(*).
- Patients who maintain clinical reactivity to egg at 5 years of age, as confirmed by oral food challenge [52] (Level of evidence II. Grade of recommendation B)(*).

Optionally, OIT can also be considered in patients who tolerate cooked egg but develop symptoms in response to small amounts of raw or undercooked egg.

Moreover, the treatment must be accepted by the patient and/or family once they have been informed of the risks and benefits of OIT and of the need for prolonged maintenance therapy (see Supplementary Materials: Appendix 1, Patient/family/tutor information and informed consent models [Spanish version]).

**The lower age limit may be waived in more severe cases, when specific IgE has not been found to decrease during successive check-ups or in patients with anaphylactic reactions owing to the lesser likeliness of spontaneous tolerance and the greater risk of severe reactions [23,24].*

(Level of evidence V. Grade of recommendation D: expert opinion).

In any case, personal and family circumstances and preferences must be taken into account, as should the resources available for administering OIT with full guarantees.

3.3.2. What patients may currently *not* be considered candidates for milk and egg OIT?

Patients with any of the following:

- Non–IgE-mediated CM and egg allergy.
- Uncontrolled asthma. In such cases, the disease must be controlled before OIT is started.
- Severe atopic dermatitis. In such cases, the disease must be controlled before OIT is started.
- A previous diagnosis of eosinophilic esophagitis.
- Inflammatory bowel disease.
- Mastocytosis.
- Immunosuppressive treatment (eg, chemotherapy, monoclonal antibodies [with the exception of omalizumab]).
- Disorders and/or treatments contraindicating epinephrine.
- Difficulty in understanding the risks and benefits of the procedure and family and social factors that complicate the long-term maintenance therapy. This includes parental conflicts, which may adversely affect treatment.
- Inability of parents to follow the instructions, identify reactions, or administer medication (epinephrine).

(Level of evidence V. Grade of recommendation D: expert opinion).

4. Milk and Egg-OIT: Build-up Phase

The build-up phase is the time between the first dose of the food and the moment at which the target dose is achieved.

Depending on the protocol used, this period may last from a few days to several months.

4.1. Requirements in Terms of Healthcare Personnel, Equipment, and Facilities: Quality and Safety Standards

OIT with food must be administered under strict safety conditions. The requirements are as follows:

- Medical personnel with experience or trained in allergology or pediatric allergology departments/units/clinics and familiarized with the procedures of OIT.
- Allergy or pediatric allergy departments/units/clinics with day hospital facilities in which the patient can be monitored after administration of the food doses scheduled during the build-up phase of OIT.
- Interventional protocols for medical and nursing personnel, appropriate space and therapeutic resources (drugs and material for cardiopulmonary resuscitation) for treating the AR derived from therapy, including severe anaphylaxis [53].
- Prolonged monitoring units (up to 24 hours) in the medical center in the event of severe anaphylaxis (in the pediatric department in the case of children).
- Safety plan for the patient or relatives, including the following:
  - Instructions on administration of CM or egg doses.
  - A written interventional protocol in the event of allergic reactions at home during OIT.
  - Rescue medication to treat allergic reactions: epinephrine autoinjectors, antihistamines, oral corticosteroids, salbutamol.
  - Forms for reporting AR and incidents during treatment
  - Availability of telematics or telephone communication allowing easy and rapid contact with the supervising physician.

The intervention plan must be revised periodically, including the epinephrine self-injection technique.

The pediatrician or general practitioner should be informed in writing that the patient is undergoing OIT and that allergic reactions may occur during administration. An explanation of the intervention plan in the event such reactions occur should also be provided.

4.2. Studies to Be Carried out Before Starting the Build-up Phase in Milk and Egg OIT

The information necessary for assessing AR risk factors, defining the treatment protocol, and studying the patient's development of tolerance is set out below.

– Clinical data:
  - Level of severity of CM or egg allergy.
  - Prior tolerance of milk or egg from other ruminants and veal.
  - Other food allergies.
  - Digestive symptoms of lactose intolerance, non–IgE-mediated allergy, or gastroesophageal reflux.
  - Bronchial asthma.
  - Atopic dermatitis.
– Immunoallergic data:
  - Results of skin prick tests with CM (milk, α-lactalbumin, β-lactoglobulin, casein) or egg (egg-white, ovalbumin, ovomucoid) protein extracts and extracts from goat and/or sheep milk.
  - Serum total and specific IgE titers against CM proteins (milk, α-lactalbumin, β-lactoglobulin, casein) or egg (egg-white, ovalbumin, ovomucoid) proteins, and goat and/or sheep milk proteins.
  - Controlled oral challenge testing with CM or cooked egg or egg white to establish the clinical responsiveness threshold. This test is not required in the case of a severe reaction after milk or egg exposure during the previous year.

4.3 Prior Conditions

– In patients with bronchial asthma or atopic dermatitis, clinical stabilization and adequate control of the disease with the required treatment are required.
– Suspected lactose intolerance needs to be confirmed.
– Patients with gastroesophageal reflux or recurrent digestive symptoms must be referred to the gastroenterologist for evaluation and the exclusion of possible eosinophilic digestive diseases.

4.4. Which Products Should Be Used?

4.4.1. Milk OIT

Currently available presentations are set out below.

4.4.1.1. Liquid milk in commercial containers

Packaged commercial milk is the preferred presentation, because this is the way milk is routinely consumed at home and it requires no preparation. It is sold pasteurized, sterilized, or ultra heat-treated. No allergenic differences have been demonstrated between these 3 presentations.

The most frequently consumed presentation is ultra heat-treated milk (5-8 seconds at 150ºC-200ºC, followed by rapid cooling). Depending on the brand and fat content, the amount of protein ranges between 2.9 g/100 mL and 3.3 g/100 mL. In order to perform OIT, an easily obtainable commercial product or brand should be used, with a protein content of about 3 g/100 mL. Using different brands of milk in the course of treatment implies possible variability in the protein doses administered. The differences between milk brands are minimal when small doses are administered; however, the patient/family must be informed of the possible variations when larger volumes are administered.

4.4.1.2. Commercial powdered milk for adults

Powdered milk is characterized by the removal of 95% of the water by atomization and evaporation processes. The protein content in this case is 34.9 g/100 g and reconstitution in 200 mL yields 7 g of proteins. This higher protein content must be taken into account when adjusting the dose during OIT. The greater advantage is that the product is long-lasting and easy to transport and store.

4.4.1.3. Should milk with or without lactose be used?

Whole milk with lactose can be used, although the patient's age must be taken into account, as the incidence of lactose intolerance increases with age, reaching a prevalence of 20%-40% in the Spanish adult population.

4.4.1.4. Processed (baked) milk

Up to 75% [54] of children with CM allergy tolerate foods prepared with milk baked at high temperatures (180ºC). In patients who do not tolerate extensively heated milk, desensitization has been attempted with this form of the product, although with little success. Most of the patients (79%) were unable to complete the treatment because of ARs, and only a limited increase in the tolerance threshold was observed in those who did complete the treatment [55].

4.4.1.5. Fermented dairy products

Only one study describes the use of yogurt from the 100 mL dose of milk in the build-up phase [56]. Fermented liquid or creamy dairy products are commonly administered in the clinical setting in Spain, usually in the last part of the build-up phase. With smaller doses, fermented dairy products are difficult to handle. The main advantage of these products is the better acceptance among patients who reject the flavor of milk and milkshakes.

4.4.1.6. Mixture of CM and goat or sheep milk

CM OIT is specific and does not guarantee tolerance to milk from other mammalian species. Up to 26% of patients who tolerate CM after OIT continue to experience reactions when coming into contact with or consuming sheep/goat milk or cheese [57] because of the lack of cross-reactivity between caprine caseins and CM caseins [58]. Consequently, once OIT has been completed, patient sensitization and evaluation of tolerance to sheep or goat milk are necessary before these can be introduced into the diet.

In order to prevent these ARs, combined immunotherapy with CM and goat and/or sheep milk in the build-up phase has been proposed. However, no data warranting their

simultaneous introduction in the build-up phases are currently available. Only one study of simultaneous milk and goat milk OIT has been published to date [59].

At present, after finishing the build-up phase of OIT with CM, there are no parameters capable of predicting the tolerance of other types of milk, except in patients with negative IgE against milk from other species or with prior tolerance to these milks.

In conclusion, the product offering most advantages is liquid CM, with or without lactose, in its commercial container.

Once the dose of 100 mL has been achieved, liquid milk may be replaced by fermented dairy products (Level of evidence V. Grade of recommendation D: expert opinion).

4.4.2. Egg OIT

Egg allergenicity is substantially modified by heating and other processes such as baking with cereal flour [60,61]. In this regard, baked egg is less allergenic than cooked egg, and the latter in turn is less allergenic than raw egg [62,63]. Therefore, the way in which the allergen source is prepared could influence the outcomes of egg OIT.

Since the egg allergens in class 1 allergy are found in egg white, this is the allergen source to be used, with or without yolk.

Dehydration, pasteurization, and freeze-drying guarantee microbiological safety and facilitate egg dosing and preservation. In vitro and in vivo studies have demonstrated allergenic equivalence to natural raw egg [63,64].

The advantages and inconveniences of the main raw egg-white products are summarized from a practical perspective in the Table 1.

Few studies have used cooked egg. The results obtained [65-69] are similar to those recorded with raw egg white, although it must be taken into account that these protocols result in tolerance to cooked egg; therefore, tolerance to raw egg white should be assessed [66].

A recent study [70] demonstrated that hydrolyzed egg is not clinically effective for achieving desensitization to cooked egg.

In conclusion, raw egg white products and cooked egg may be effective in achieving desensitization, although further studies with cooked egg are needed to compare its efficacy with that of the raw food.

If the objective to achieve tolerance only to cooked egg, desensitization with heated egg with or without small amounts of raw egg will suffice (Level of evidence V. Grade of recommendation D: expert opinion).

4.5. What Dose Should Be Reached?

4.5.1. Milk OIT

The aim of milk OIT is to allow the allergic patient to follow a diet free of restrictions with regard to this food in its different presentations. However, the goal of the build-up phase must be to achieve tolerance to the previous target dose.

Published protocols for milk OIT show the most frequently proposed dose to be 200 mL. This amount can be consumed in a single dose, or in several fractions during the day. However, some protocols establish a target dose of up to 250 mL. These amounts represent between 6 g and 7.5 g of milk and are considered to be the normal liquid milk intake for nonallergic individuals in our setting. Tolerance to this dose is considered complete desensitization, while lower doses could represent partial desensitization.

With regard to the consumption of cheese made from CM, the protein concentration of the different varieties must be taken into account (see Supplementary Materials: Table 2).

In patients sensitized to milk proteins from other species (eg, goat, sheep, and buffalo), tolerance must be evaluated through controlled challenge tests before introduction in the diet, except in the case of tolerance to these milks prior to CM OIT.

In patients with risk factors (see Section 6.1), a final milk dose of 15 mL may be considered, as it could offer protection against minor accidental exposures and raise the tolerance threshold over time [71] (Level of evidence V. Grade of recommendation D: expert opinion).

4.5.2. Egg OIT

The choice of outcome or target for OIT should be based on the preferences of the patient, parents, or guardians after having provided sufficient information on the chances for successful desensitization to a normal serving. This outcome can in turn be modified according to the evolution of the desensitization process, with the aim of seeking a less ambitious target with lower egg doses. In this regard, the main concern is to protect the patient against possible ARs upon accidental exposure to the food.

Table 1. Advantages and Disadvantages of the Different Raw Egg-White Products Used in Oral Immunotherapy

Product	Raw Egg White	Pasteurized Egg White	Commercial Dehydrated Egg White	Freeze-Dried Egg White
Advantages	Availability Low cost	Microbiological safety Easy dosing Low cost	Microbiological safety Precise dosing Storage without refrigeration	Microbiological safety Storage without refrigeration
Disadvantages	Contamination risk Difficult handling and dosing	Expiry within a few days Need for refrigeration	Greater cost Pre-established doses More complex dosing in case of changes in protocol	No commercial formulation available More difficult dosing

We thus may establish 3 OIT outcomes associated with different maximum doses, as follows:

– Protection against traces or cross-contamination in patients who do not tolerate baked egg with flour.
– A diet containing cooked egg, with restriction of raw egg.
– A normal diet without restrictions.

4.5.2.1. Protection against traces or cross-contamination

Only 1 study has considered protection against traces or cross-contamination [72], suggesting that a 300-mg dose of powdered egg white or its equivalent would suffice to maintain protection against accidental ingestion due to traces, cross-contamination, or labeling error, and even against the amount of egg contained in an average-size pastry.

4.5.2.2. Normal diet without restrictions

Most OIT protocols with egg are programmed to achieve desensitization to a normal serving, ie, 1 whole egg [73-77], which represents tolerance to about 30 mL of egg white, 45-50 mL of whole egg, 10 g of pasteurized whole egg [77], or 3.6 g of egg-white proteins [78-80], thus reflecting the protein content of the egg white in a medium to large egg.

Although some studies [52,72] suggest that desensitization to low or medium doses guarantees desensitization to high doses over the middle to long term in a high percentage of patients, the usual practice is to seek tolerance to a whole egg or egg white in order to normalize the diet within weeks or a few months.

In conclusion, the maximum dose to be reached at the end of the build-up phase depends on the intended outcome of therapy, which in turn is conditioned by the severity and personal preferences of the patient after providing him or her with the necessary information. In addition, tolerance to a whole egg or egg white is necessary in order to be able to follow a normal diet. Furthermore, if the aim is tolerance only to cooked egg, the patient must be warned of the need to avoid raw or undercooked egg. Finally, if the aim is to protect against accidental exposure, a 2.2-mL dose of raw egg white or its equivalent may be established, although further studies are needed in this regard (Level of evidence V. Grade of recommendation D: expert opinion).

4.6. Which Dose Increments Are Safest? At What Rate?

4.6.1. Milk OIT

Few studies have compared the efficacy and safety of the various proposed milk dose increments. A Spanish study in children with strong sensitization and manifestations of anaphylaxis showed that a protocol comprising dose increments of no more than 20% increased the safety of treatment [81].

It is advisable to administer the dose on a full stomach and avoid intense physical exercise in the following 2-3 hours (Level of evidence V. Grade of recommendation D: expert opinion).

4.6.2. Egg OIT

The largest dose increments are associated with an increase in ARs [37,73,82].

Rush protocols and intermediate or slow protocols have been described, each with different time intervals. Dose escalation is usually carried out weekly [52,56,77,79,83], although some authors introduce dose increments every 1-3 days [64,65,74] or every 2 weeks [37,52,72,78]. There have been reports of cluster or rush protocols [66,67] lasting 12 and 5 days.

In conclusion, currently available data suggest that protocols involving proportionally lower dose increments may be safer both when administered at greater intervals (every 1-2 weeks) and when carried out on a daily basis. The dose escalation rate therefore does not seem to affect the safety of the procedure (Level of evidence II. Grade of recommendation B).

4.7. Are Rush/Cluster Protocols in Milk OIT and Egg OIT Safe? In Which Patients Can They Be Used?

Almost all protocols use a cluster protocol in the first 1-2 days. Successive doses are administered every 30-60 minutes, with increments that vary between 50% and 100%, depending on the protocol used. In general, the doses administered during these first days are lower than the response threshold of the patient.

Few studies have been published on OIT rush protocols with CM, which are completed in a period of 3-7 days. A total of 32 children with CM allergy have been treated, with good results (complete desensitization in 59% and partial desensitization in 31% of cases); allergic reactions similar to those observed with the standard protocols have been reported [56,84-86].

Published rush protocols with egg are also scarce [66,67] and have been carried out by combining pasteurized or dehydrated egg white with cooked egg. The reported efficacy rates were 86.9% and 100%, respectively, although a maximum dose of 1 whole cooked egg was reached. The results obtained with these protocols are similar to those reported for more prolonged protocols [69,79,80,87,88], with efficacy rates of between 82% and 93%, reaching maximum protein amounts equivalent to 1 whole egg white.

No studies have compared the safety profile of rush protocols with slow protocols in egg OIT. Studies involving rush protocols [66,67] describe mild and moderate ARs in 78% and 100% of patients, respectively, although the reported dropout rates were no greater than in the case of the slow protocols. Later studies [61,66] suggested the use of rush protocols in less severely affected patients and only in weakly sensitized individuals, ie, those with sIgE to egg white <22 kU_A/L and to ovomucoid <12 kU_A/L.

The advantage of rush protocols is that they allow the specialist to have direct control of the entire build-up phase (ie, without home-administered doses), up to the maximum maintenance dose, with increased control over the cofactors (eg, physical exercise, infections, and gastroenteritis).

In conclusion, published rush protocols have been found to be effective and relatively fast. Their safety profile is similar to that of the published slower protocols. Rush protocols may be useful in less severely affected patients without risk factors for ARs (Level of evidence V. Grade of recommendation D: expert opinion).

4.8. What Should the Starting Dose Be? Are Fixed Starting Doses for The Build-up Phase Preferred, or Should the Doses Be Individualized?

Although protocols involving fixed doses are the most frequently used option, individualized doses can also be administered, by starting the build-up phase according to the results obtained in the baseline oral challenge test.

In the few studies that have described the use of protocols with individualized starting doses, the doses range between 10% and 50% of the threshold dose [89] or start with the last tolerated dose in the oral challenge test [80,90].

Individualized protocols may be indicated in patients who have reacted to medium or high doses of the food in the challenge tests, with the advantage that the build-up phase can be shortened, with lower consumption of healthcare resources and greater patient convenience; however, the build-up starting dose in relation to the threshold dose has not been established. Although this concept is not well defined, a cumulative dose of half a boiled egg or ≤50 mL of milk may be considered a medium to high tolerance threshold) (Level of evidence V. Grade of recommendation D: expert opinion).

4.9. Are There any Distinguishing Features of the ARs That Manifest During Milk OIT and Egg OIT? Are Some Types of Reaction More Frequent Than Others?

Abdominal pain is a frequent symptom and cause of patient withdrawal in egg OIT [52,77,91]. It may be more common than skin symptoms [40] and, in some cases, it is associated with diarrhea and/or vomiting.

Gastrointestinal reactions may be of such intensity and duration that they prove refractory to treatment (eg, corticosteroids and antihistamines). Some authors consider abdominal pain a specific reaction and no longer classify it as mild when it lasts more than 15 minutes, requires the patient to lie down, or causes skin paleness or tachycardia [92]. In these cases, treatment with epinephrine has been assessed. The favorable experience gained with this drug has led a number of authors to advocate the use of this drug, although no studies have been published. Epinephrine leads to rapid resolution of these associated problems, which often limit the progress of OIT.

No particular or distinguishing ARs have been reported during milk OIT.

4.10. Are Antihistamines, Disodium Cromoglycate, Montelukast, and/or Ketotifen Effective in Preventing ARs During the Build-up Phase of OIT With Food?

It is not clear whether the prophylactic administration of antihistamines or other drugs is useful in preventing ARs during the build-up phase of OIT with food. Although conducted in patients with allergy to peanut, a simple-blind, placebo-controlled study compared a group premedicated with ketotifen versus placebo [93], and recorded a decrease in the number of gastrointestinal ARs in the ketotifen group. Likewise, a retrospective study with only 5 patients [94] evaluated the use of montelukast during OIT and found the drug to be useful in preventing abdominal pain.

In conclusion, current evidence is insufficient to allow the generalized recommendation of these drugs for the prevention of ARs during the build-up phase of OIT with food, although they could be used when adverse effects complicate continuation of treatment.

4.11. General Recommendations in the Build-up Phase

Administer the dose with food.

Avoid physical exercise in the 2-3 hours after dosing and nonsteroidal anti-inflammatory drugs in the 2-3 hours around food ingestion.

In the event of an intercurrent disease:

- Asthma attack: 50% reduction of the dose.
- Gastroenteritis: 50% reduction of the dose or suspension during the acute phase of the disease for a maximum of 3 days, followed by resumption under observation in hospital with 50% reduction of the dose.
- Febrile upper airway infection: return to the previous tolerated dose.

(Level of evidence V. Grade of recommendation D: expert opinion).

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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