

Oral Immunotherapy for Food Allergy: A Spanish Guideline. Egg and Milk Immunotherapy Spanish Guide (ITEMS GUIDE). Part II: Maintenance Phase of Cow Milk (CM) and Egg Oral Immunotherapy (OIT), Special Treatment Dosing Schedules. Models of Dosing Schedules of OIT With CM and Egg

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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.

5. Maintenance Phase of Cow Milk and Egg Oral Immunotherapy

The maintenance phase of OIT follows the build-up phase. Its length has not been defined, although it may cover months to several years.

5.1. Food Forms to Be Used

5.1.1. Cow Milk

The CM used during this phase is the same liquid pasteurized or UHT milk, with or without lactose, as that used in the build-up phase. Other dairy products can be used, taking into account their respective protein concentrations, in order to ensure that the dose administered is equivalent to that afforded by liquid milk (see Part I, Supplementary Material, Table 2).

5.1.2. Egg

Once the product for the build-up phase has been chosen, it should also be used during the maintenance phase, except in cases of poor tolerance or patient rejection. Such situations should be duly evaluated, and a change of product should be considered.

Maintenance therapy can be provided with the maximum tolerated dose and with the same allergen source (raw or cooked) as used in the build-up phase or with an equivalent source.

If pasteurized or dehydrated egg white is used during the build-up phase, regular intake of egg in its usual presentations (eg, omelet, fried, scrambled, and boiled) must be ensured before replacing the egg product during maintenance.

The use of cooked egg during the maintenance phase of OIT can be useful in patients with severe egg allergy or in those cases where OIT with raw egg or raw egg products has failed. If cooked egg is chosen for the maintenance phase, it is important to note that reactions may result from the intake of foods containing raw egg (eg, sauces, creams, and ice cream) [1,2]. However, this strategy may suffice from a practical point of view, by making it possible to open the diet to those foods that contain egg in its usual presentations (see Part 1, section D.4.2). If this option is chosen, tolerance of raw egg white must be periodically assessed. On the other hand, if an undercooked form of the food is chosen, possible aversion or rejection and a decrease in regular intake of the food, particularly during the first year of treatment, appear to be the factors most closely associated with loss of sensitization or failure of OIT.

Conclusions

- The CM used during this phase is liquid pasteurized or UHT milk, with or without lactose.
- In the case of dairy products (yogurts or cheeses made from CM) administered in the maintenance phase, the possible differences in allergenicity and protein contents with respect to CM must be taken into account.
- Maintenance therapy in OIT with egg can be provided with the same allergen source (raw or cooked) as used in the build-up phase or with an equivalent source.
- Data are contradictory as to whether the use of cooked egg during the maintenance phase is able or not to

maintain the desensitization achieved with raw egg white in quantities similar to those tolerated at the end of the build-up phase.

- Patient aversion to or rejection of egg must be assessed, and the clinician must decide whether or not to replace these forms with the regular administration of egg products (pasteurized or dehydrated).

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

5.2. Dosing Schedules

5.2.1. Cow Milk

5.2.1.1. What are the proposed doses in the maintenance phase of milk OIT? Equivalent to a full serving of milk or smaller doses?

- In patients who reach the maximum dose of 200 mL during the build-up phase, a daily dose of 200 mL of milk is advised during the maintenance phase [3-6].
- Patients who reach a dose of 200 mL during the build-up phase can consume milk or dairy products up to that amount or the equivalent, in addition to the scheduled maintenance dose. However, patients are to be instructed not to consume these foods during the 2 hours before and after administration of the established maintenance dose. The aim of this measure is to avoid a high cumulative dose, which could cause a reaction.

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

5.2.1.2. In the case of lower doses than a full serving of milk, should periodic challenge testing be considered for assessment of possible changes in the threshold?

- When the patient is unable to reach a dose equivalent to a full serving of milk, maintenance therapy should be administered with the maximum dose reached during the build-up phase. The regular intake of lower doses than a full serving of milk helps to increase the threshold [7]. In this case, the increase in threshold should be checked periodically by means of oral food challenges.

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

5.2.1.3. What is the recommended frequency of food intake in the maintenance phase of milk OIT? What is the best time of day to administer doses? Should the milk be administered under fasting conditions or with other foods?

- In practically all studies of milk OIT, daily doses are administered during the maintenance phase. There is no evidence to recommend less frequent dosing. Lesser dosing frequencies may result in a loss of the desensitization effect.
- No differences in the frequency of adverse reactions (ARs) have been observed on comparing dosing schedules comprising daily doses versus dosing schedules involving 2 weekly doses [8].
- A decrease in dosing frequency, or a lack of adherence to therapy, could result in an increased number of ARs [9]. If reducing the dosing frequency or temporarily

- suspending treatment is intended, the following dose should be administered under medical supervision owing to the risk of an allergic reaction.
- The attending physician should be informed if the patient stops consuming milk for more than 3 consecutive days in order to decide whether the next dose should be administered under supervision.
 - The family should choose a time of day when caregivers can supervise the patient and subsequent intense physical exercise is avoided [10].
 - Although there are no data on the effect of fasting on the safety of OIT with CM, most studies recommend against administration of the dose after fasting, as this may result in rapid allergen absorption and an increased risk of allergic reactions. While this strategy seems reasonable, there is no clear evidence of the impact of fasting on the safety of OIT [10].
- (Level of evidence V. Grade of recommendation D: expert opinion).

5.2.2. Egg

5.2.2.1. What are the proposed doses in the maintenance phase of egg OIT? Equivalent to a full serving dose or lower doses? In the case of doses that are lower than a full serving of egg, should periodic challenge testing be considered for assessment of possible changes in the threshold?

- The egg dose during the maintenance phase should be the maximum dose reached in the build-up phase and using an egg product of similar allergenicity.
- When the dose administered during the maintenance phase is lower than a full serving dose equivalent to 1 egg—whether raw or cooked—the tolerance of doses equivalent to 1 egg should be checked by an oral food challenge.

(Level of evidence IV. Grade of recommendation C)

5.2.2.2. What is the recommended frequency of food intake in the maintenance phase of egg OIT? What is the best time of day to administer the doses? Should the egg be administered under fasting conditions or with other foods?

- Between 71% and 90% of all patients in the maintenance phase of OIT with egg retain desensitization after 1-6 years of follow-up [11-15]. Maintenance therapy in OIT with egg can be carried out in the form of daily intake of the food or dosing at least 3 times a week.
- More frequent egg consumption during the maintenance phase favors the maintenance of desensitization [14].
- The egg dosing frequency during the maintenance phase should be reduced under medical supervision, since allergic reactions may occur [10,14].
- Discontinuous egg intake (less than 3 times a week) following the build-up phase may be a cause of allergic reactions during maintenance [10].
- The attending physician should be informed if the patient stops consuming egg for more than 6 consecutive days in order to decide whether the next dose should be administered under adequate supervision.

- There is no evidence that a specific time of day is best for administering the egg dose.
- Although there are no data on the effect of fasting on the safety of OIT with egg, it is advisable to avoid fasting, since it may increase the risk of allergic reactions.

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

5.3. Control and Management of Adverse Reactions During Oral Immunotherapy

5.3.1. How should ARs be managed during the maintenance phase of OIT? What cofactors or triggering factors should be controlled or avoided during the maintenance phase?

The treatment of AR during the maintenance phase is the same as during the build-up phase and is based on the corresponding management guidelines [15].

Reactions during this phase may be related to poor adherence to therapy [9,14,16] or to the action of cofactors. Risk factors for systemic reactions during the maintenance phase of OIT include physical activity following intake of the food [9,17-20], infectious processes [9,21], and uncontrolled asthma. Nonsteroidal anti-inflammatory drugs may act as cofactors in certain patients. Other cofactors such as stress, menstruation, or allergic rhinitis caused by aeroallergens have also been described [9,14]. In any case, some of the reactions observed during the maintenance phase may prove unpredictable, with no relation to cofactors.

Conclusions

- Patients and their caregivers must be trained to adequately recognize and deal with the reactions that may develop during OIT (see Part 1, section 4.1.).
 - Reactions during the maintenance phase of OIT may be related to poor adherence to therapy or to the action of cofactors, although in some cases, no triggering factors are identified.
 - Risk factors for systemic reactions during OIT include physical exercise following intake of the food, infectious processes, uncontrolled asthma, nonsteroidal anti-inflammatory drugs, stress, menstruation, and allergic rhinitis caused by aeroallergens.
 - Any associated allergic disorders such as rhinitis, asthma, and/or atopic dermatitis must be controlled in order to reduce the risk of exacerbation of such problems after administration of the OIT doses. Periodic evaluation of the need for medication or dose adjustment to control such disorders is required, according to the needs of each patient.
- (Level of evidence IV. Grade of recommendation C).

5.3.2. What are the criteria for modifying the maintenance dose in the event of ARs during the OIT maintenance phase?

Some publications [10,14,23] describe the steps taken in the event of ARs during the build-up phase and which are extendable to the maintenance phase.

- Mild reactions: OIT can continue when the patient is asymptomatic, with repetition of the same dose the following day.

- Moderate reactions: OIT can continue the following day with a lower dose.
 - Severe reactions: The interruption of OIT or dose reduction should be considered.
- (Level of evidence IV. Grade of recommendation C)

5.4. Duration of Maintenance Treatment

What is the minimum duration of the CM and egg OIT maintenance phase?

There are few studies on the long-term outcome of OIT, and no evidence has been published on the minimum duration of the maintenance phase.

In milk OIT, the duration of follow-up reported in the literature ranges from 3 to 5.8 years. Desensitization to a full serving dose of CM equivalent to 200 mL is maintained in a broad range of between 31% and 100% of patients [6,21,24,25]. Published data indicate that the long-term outcomes of OIT are heterogeneous: some patients lose desensitization status in the long term, while others can continue to consume doses equivalent to a full serving or lower doses without developing symptoms [24]. A number of factors have been associated with favorable long-term outcomes, as follows: serum baseline milk sIgE, onset of gastrointestinal and respiratory symptoms during OIT, the threshold dose in challenge testing performed after 3 months of maintenance therapy, the amount of milk recommended each day, and the outcome of the milk skin prick tests performed during the course of the maintenance phase.

Two studies on egg OIT evaluated the efficacy of treatment during the maintenance phase [1,2]. In both cases, the efficacy of OIT in inducing desensitization to raw egg was found to decrease with respect to the build-up phase to 54% and 50% after 6 and 9 months of maintenance, respectively [1,2]. This decrease in efficacy could be attributable to the use of cooked egg during this phase, in place of the raw egg regularly administered during the build-up phase. In contrast, other studies have found that after completion of the build-up phase of egg OIT, up to 90% of patients can consume the food without restrictions after 3-6 years of follow-up [11].

Conclusions

- No evidence has been published on the required minimum duration of the maintenance phase of OIT.
- With respect to the minimum duration of the maintenance phase, and taking into account the lack of further data, the criteria established for immunotherapy with venoms and aeroallergens can be followed, with prolongation for at least 5 years, provided there have been no ARs in the last 2 years.

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

5.5. Assessment of Permanent Tolerance or Sustained Unresponsiveness

5.5.1. Should a minimum length of the maintenance phase be considered to study permanent tolerance in a patient receiving CM and egg OIT?

Some studies have evaluated permanent tolerance status based on an oral food challenge following an avoidance diet

at the end of OIT. The data obtained to date from studies on permanent tolerance after OIT are not fully satisfactory.

Keet et al [24] found that 27% of the patients initially included in their study (8/30 individuals) reached permanent tolerance to CM after a post-OIT avoidance period of 6 weeks [24].

In the study by Staden et al [20], 75% of responders (9/12 individuals) who had successfully completed milk or egg OIT exhibited permanent tolerance (2 months of avoidance diet) after 18-24 months.

Studies on egg OIT that examined the achievement of permanent tolerance report incidences of permanent tolerance after OIT of 28%-75%, with very long maintenance periods of 3-36 months [26-30]. Aspects such as the duration of the maintenance phase, the optimum food dose for that phase, and baseline egg sIgE appear to condition the achievement of permanent tolerance and could account for the different frequencies reported [31].

5.5.2. How long should the patient maintain the avoidance diet before performing the oral food challenge?

Most studies report avoidance periods of 1-2 months [9,10,32,33], and in 2 reports the period was extended to 3-4 months [34,35]. However, it is not clear whether longer avoidance periods guarantee tolerance of the food. In this regard, a study of peanut OIT found that 50% of patients (3/6 individuals) who passed a first challenge test after 3 months of avoidance diet following successful completion of OIT had a positive second challenge test after the avoidance period was extended for another 3 months [36].

5.5.3. Can sIgE in the course of maintenance therapy act as a marker of permanent tolerance?

High baseline sIgE at the initiation of OIT has been correlated with serious ARs and a low frequency of desensitization in children, in both the build-up phase and the maintenance phase [37], whereas low baseline egg and ovomucoid sIgE have been associated with the development of permanent tolerance [38]. sIgE tends to decrease very slowly, remaining stable or increasing on reaching the maximum tolerated amount of food, followed by a decrease during the subsequent 12-18 months [34,39].

The decrease in milk or egg sIgE is correlated with the success of desensitization [33] and the achievement of permanent tolerance [9], whereas constant or increasing sIgE levels are predictive of persistent allergy throughout OIT [31]. Some studies have found that sIgE levels decrease during OIT [4,10,29,30,40,41], whereas others recorded no changes [8,42-44]. Nevertheless, these immunological variables were not correlated with permanent tolerance in other publications [25].

Changes in the titers of egg sIgE in the course of OIT can be used as a predictor of permanent tolerance. In this regard, cut-off points for egg sIgE have been identified—7.1 kU_A/L for egg white and 1.7 kU_A/L for ovomucoid—to predict the challenge test outcome after OIT and an avoidance period of 1 month. The probability of a positive challenge test in the

presence of titers above the cut-off point was found to be 90% and 73%, respectively [33].

Conclusions

- Results obtained to date for the achievement of permanent tolerance or sustained unresponsiveness after OIT followed by a food avoidance phase are not fully satisfactory.
- Further studies are needed to define the duration of the maintenance phase and the optimum food doses in order to ensure permanent tolerance, with the identification of predictors to establish the best moment for assessing the achievement of this state through changes in sIgE levels over the course of OIT.
- Evaluation of the development of permanent tolerance implies the need for a strict exclusion diet over a period of 1-4 months, followed by oral food challenge under medical supervision. It is not clear whether avoidance periods of more than 4 months affect permanent tolerance.
- Knowing whether a patient has achieved permanent tolerance can have important practical consequences; the patient and his/her family should therefore be informed about the advantages and disadvantages of performing this evaluation.

(Level of evidence IV. Grade of recommendation C)

5.6. Long-Term Follow-Up: Required Duration

How long must follow-up be maintained in patients receiving maintenance treatment in the context of CM and egg OIT?

As indicated in the section on duration of treatment, few studies are available on the long-term outcome of OIT, and the follow-up periods range between 1 and 6 years [1,2,6,11,36,38,45]. In the long term, desensitization status at a dose equivalent to a full serving of food is maintained in a variable percentage of individuals. Some patients lose desensitization over the long term, and others can continue to consume lower doses without developing symptoms [37].

Since ARs are more frequent during the first months of the maintenance phase [23], closer monitoring during that period would therefore be advisable.

Conclusions

- Long-term, and even indefinite, patient follow-up is needed in order to assess the safety of treatment.
- Follow-up should continue until the patient has lost sensitization to the food, as confirmed by negative skin prick test and specific IgE results, or at least until permanent tolerance has been confirmed after a food avoidance period of at least 4 weeks. Achievement of permanent tolerance will be confirmed when considered opportune by the supervising physician, after assessing the risks and benefits in agreement with the patient and caregivers.

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

5.7. Clinical and Immunological Controls

What clinical and immunological controls are required in patients receiving CM and egg OIT, and how often should they be performed?

Patients must be evaluated periodically after OIT. In this regard, most studies conduct follow-up determinations every 6 months during the first 18 months [30] or the first 3 years. In clinical practice, most authors perform controls with skin prick tests and determination of CM and egg sIgE and/or their proteins, as well as IgG4 at each control [1,6,21,30,43].

In the course of clinical follow-up, it is essential to monitor regular food intake and acceptance of the recommended food doses.

sIgE levels may prove useful for assessing progression towards permanent tolerance [33].

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

Conclusions

- During the follow-up of patients undergoing OIT, clinical assessment is required 1 month after completing OIT, and then every 6 months during the first year and every 12 months from the second year onwards.
- Skin prick tests and measurement of serum total and specific IgE levels to CM and/or egg are recommended at the end of the build-up phase and then every 12 months. In those centers where the required techniques are available, periodic measurements of specific IgG4 toCM and/or egg are indicated throughout the follow-up period.

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

6. Special Dosing Schedules in Milk and Egg OIT

6.1. Identification of Patients at Risk of ARs and Failure of OIT

6.1.1. What clinical criteria enable identification of patients at risk of AR and failure of OIT?

6.1.1.1. Previous anaphylactic reactions to the food

Most studies indicate that patients with previous anaphylactic reactions will experience more reactions during OIT and will have a greater probability of treatment failure [39,46,47].

6.1.1.2. Coexistence with asthma

In anaphylaxis, the coexistence of asthma is a risk factor associated with fatal anaphylactic reactions, particularly in severe and uncontrolled asthma [15].

Asthma is the most important risk factor interfering with the development of OIT, causing more severe and persistent ARs during treatment, particularly in cases of moderate-severe asthma [10,17,22,31,46,48-52].

6.1.1.3. Adolescence

The peculiar characteristics of adolescence (poor adherence to therapy, scant awareness of the risks of OIT) are risk factors for severe reactions.

Another major cofactor in the onset of ARs is the high prevalence of respiratory allergic disease in adolescents with food allergy. Asthma in these cases is more severe [9,31,24] and in some cases poorly controlled because of the above-mentioned factors and frequent intense physical activity.

6.1.2. What biological criteria enable identification of patients at risk of AR and failure with OIT?

6.1.2.1. Magnitude of the result of baseline skin prick testing

The results of studies on milk OIT indicate the following:

- Skin prick testing with CM diluted to 1/1000 and yielding wheals >5 mm constitutes a risk factor for an indolent course (OR, 8.3; 95%CI, 1.9-35.5) [53].
- Patients are at a high risk of recurrent ARs during OIT in the presence of 2 or 3 of the following factors: skin prick test results with CM yielding wheals >9 mm, IgE levels >50 kU_A/L, and grade 2, 3, and 4 reactions to challenge testing [17].

There have been no studies in egg OIT about the relationship between wheal size in skin prick testing with egg and the risk of AR.

6.1.2.2. Baseline serum specific IgE levels

The results of milk OIT studies indicate the following:

- Baseline milk-IgE levels are greater in children in whom treatment fails than in those in whom desensitization is achieved ($P<.05$) [38].
- Patients with baseline milk sIgE >50 kU_A/L experienced more severe, less predictable, and more persistent frequent reactions, or their OIT failed [6].
- Patients with milk sIgE levels >75 kU_A/L have a poorer long-term prognosis in terms of treatment failure and reductions in tolerated milk dose [8].
- Milk and casein sIgE levels ≥ 17.5 kU_A/L increased the risk of an indolent course with OIT, independently of patient age, sex, or comorbidities such as asthma [53].
- The baseline differences in recognition of IgE by linear milk peptides could constitute a marker of risk for AR and failure of OIT [40,54].

The results of egg OIT studies indicate the following:

- Ovomucoid sIgE levels <8.85 kU_A/L are predictive of successful OIT. Higher titers are associated with a 95% probability of more frequent ARs that persist over time and of early withdrawal [10].

6.1.2.3. Symptom-triggering dose in milk and egg challenge tests before OIT

Patients with poorer OIT outcomes are those with positive challenge test results at lower doses, although the doses that may be regarded as low have not been established to date [43]. The doses related to ARs and failure of milk OIT range from 1 mL to 2.5 mL [17,18,22]. As for egg OIT, the dose is approximately 1 mL of raw egg white [2,14,47] and a quarter of cooked egg white [10].

6.1.2.3. Risk factors for AR and OIT failure. Conclusions

- Previous and recent clinical manifestations of food-related anaphylaxis.
(Level of evidence II. Grade of recommendation B).
- Coexistence with moderate or severe asthma.
(Level of evidence II. Grade of recommendation B).
- High baseline specific IgE levels. Although no cut-off points have been established, we recommend reference levels of 17.5 kU_A/L for casein and 8.8 kU_A/L for

ovomucoid, which could be modified in the future on the basis of strong evidence.

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

- Low oral food challenge test threshold. Although no cut-off points have been established, we recommend reference levels of 1 mL of pasteurized egg white or a quarter of cooked egg white, and 2.5 mL of milk, which could be modified in the future.

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

Although adolescence in itself does not constitute a risk factor, closer supervision and education measures are required in adolescent patients in view of the circumstances that characterize this stage in life. (Level of evidence V. Grade of recommendation D: expert opinion).

6.2. Improving Safety in Patients at Risk

6.2.1. Would it be advisable to apply OIT with smaller dose increments and over a longer period?

Small dose increments in egg OIT [14] and maintenance with small doses such as 300 mg of egg white protein [32,34] or 15 mL of CM [55] could help to increase the threshold and represent an alternative dosing schedule in patients at risk.

6.2.2. Sublingual immunotherapy with CM or egg

6.2.2.1. Is it effective and safe?

Placebo-controlled studies involving sublingual immunotherapy (SLIT) in patients with allergy to kiwi [56], peanut [57-61], CM [66,67], hazelnut [64], and Pru p 3 extract from peach [65], as well as other studies [63,66], have reported a better safety profile for SLIT than for OIT, albeit with comparatively lower efficacy or with no differences in comparison with placebo, as shown in a study with peanut [59]. No studies have been published on egg SLIT.

6.2.2.2. Should the SLIT dose be spat out or swallowed?

SLIT with food follows the same technique as SLIT with allergens.

Swallowing the dose should be avoided until the oral threshold exceeds the sublingual dose administered. This is particularly important in patients with clinical manifestations of anaphylaxis.

6.2.2.3. When to use SLIT: as pretreatment or cotreatment with OIT?

It has been suggested that pretreatment with SLIT followed by OIT could benefit the safety and efficacy profile of OIT [67]. One study examined OIT and previous cotreatment with peanut SLIT. This strategy was seen to afford substantially greater protection against AR than OIT alone [61].

6.2.2.4. What CM dose should be administered in SLIT?

The SLIT dosing schedules generally include an initial build-up phase and a maintenance dose. The doses are small, ranging from micrograms to milligrams of CM protein [65], generally 1-6 mg/protein/dose/day [58-62,64,66], although doses of up to 32 mg (1 mL) have been tolerated [63]. The

maximum tolerable volume appears to be 1 mL, ie, the maximum amount used in the aforementioned studies.

6.2.3. Treatment with omalizumab during OIT

6.2.3.1. Is omalizumab effective in reducing the number and severity of ARs?

Treatment with omalizumab reduces serum free IgE levels, resulting in a loss of Fc ϵ receptors in mast cells, basophils, and antigen-presenting cells [68]. Omalizumab has been shown to increase the threshold in patients with food allergy [69]. For this reason, it has been used in combination with OIT in order to shorten dosing schedules and reduce the number and severity of ARs. Adjuvant omalizumab is effective in improving the safety profile of OIT and reducing the number and severity of ARs, particularly in highly sensitized patients with a history of anaphylaxis, and is effective in patients in whom such therapy had previously failed because of ARs [70-80].

6.2.3.2. What doses and frequencies of administration should be used?

The omalizumab dosing and administration intervals proposed for the treatment of severe allergic asthma are calculated based on total IgE levels and patient weight according to the Summary of Product Characteristics [71,73,74,76-78,80]. If serum IgE levels exceed 700 kU_A/L, the dose is calculated by applying the formula 0.016 mg/kg/IgE (kU_A/L) [76] with a maximum dose of 600 mg every 2 weeks [77].

6.2.3.3. What omalizumab administration schedule should be used?

Most studies make use of pretreatment dosing schedules, administering omalizumab before starting OIT for a period ranging from 4 to 18 weeks [72-80].

Starting omalizumab 9 weeks before OIT [76,81] seems sufficient to achieve the maximum effect in terms of free serum IgE reduction (7 days) and high-affinity receptors of basophils (7 days) and mast cells (70 days) [81].

The use of the drug is therefore not limited to pretreatment and cotreatment with OIT. The introduction of omalizumab at any time during OIT has been evaluated as rescue therapy [78].

Data on the best time to stop omalizumab after reaching the maximum OIT dose vary considerably (1-19 months) [74,76,77,80,82], although in most studies the drug is discontinued 1-2 months after concluding OIT [74,76,82].

6.2.3.4. Does suspending omalizumab after OIT increase the risk of serious ARs?

Immediate tolerance after suspension of omalizumab is variable. In one study, 100% of patients who reached the maintenance dose were able to continue to consume milk after suspension [76]. In the case of peanut, the percentage was 90% [72], and patients seemed able to continue to take the food with no symptoms or only mild and tolerable symptoms following suspension [73,74,82]. However, a proportion of the patients (33%-60%) experienced a relapse, with a drop in the clinical responsiveness threshold 2-4 months after suspending omalizumab [80,83]. The difference may lie in the degree of clinical responsiveness and sensitization of the patients.

Furthermore, studies in which the length of follow-up is prolonged have documented a relapse in terms of reappearance of symptoms with the food over time without omalizumab. Between 6 and 8 months after suspension of omalizumab, reactions appear in up to 50% of patients. Most of these reactions are mild, although some patients experience severe reactions requiring epinephrine [76]. These observations suggest that it is necessary to increase the duration of maintenance treatment with omalizumab and point to the need for further studies to help define the adequate length of such therapy.

Treatment with omalizumab does not alter progression towards persistent or sustained tolerance, as evidenced by the results of a recent randomized, double-blind, placebo-controlled study. The suspension of omalizumab, followed by a milk avoidance diet for 8 weeks, did not result in significant differences in the development of sustained tolerance (48.1% in the active treatment group with omalizumab vs 35.7% in the case of placebo) [78].

Therapeutic strategies for increasing safety Conclusions

– Smaller dose increments

The dose increments should be optimized, ie, reduced to minimize the possible adverse effects of treatment and increase efficacy.

(Level of evidence III. Grade of recommendation C).

– Previous cotreatment with sublingual immunotherapy

SLIT is accepted as a potential treatment for favoring desensitization to some foods. Benefits in terms of both immunological parameters and efficacy have been documented, although to a lesser extent than with OIT. In contrast, SLIT is associated with a lower incidence of systemic adverse effects than OIT.

(Level of evidence II. Grade of recommendation B).

Although SLIT alone is not more effective than OIT, it should be considered a coadjvant to OIT.

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

Pretreatment with SLIT should last at least 6 weeks before initiation of OIT, although it may subsequently be maintained as cotreatment with OIT.

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

The recommended maximum dose would be 1 mL of CM and 1 mL of the 1/10 dilution, starting with lower doses and gradually increasing the dose in patients who are highly sensitized and/or present clinical manifestations of anaphylaxis.

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

Omalizumab as an adjunct to OIT

There is evidence of the usefulness of omalizumab in reducing ARs and their severity (Level of evidence I. Grade of recommendation A). The drug would therefore be particularly indicated in patients who are highly sensitized, with clinical manifestations of anaphylaxis, and in whom previous OIT has failed.

The recommendation is to use the omalizumab dose and administration interval corresponding to the total IgE levels

and weight of the patient according to the Summary of Product Characteristics for the treatment of severe allergic asthma. Alternatively, the formula 0.016 mg/kg/IgE (kU_A/L) can be applied, with a maximum dose of 600 mg every 2 weeks. (Level of evidence V. Grade of recommendation D: expert opinion).

Omalizumab should first be administered as pretreatment for no less than 4 weeks before the start of OIT, the recommendation being 9 weeks before the start of omalizumab (Level of evidence V. Grade of recommendation D: expert opinion).

On the basis of the available data, no recommendations can be made regarding dose reduction or the interruption of omalizumab in patients receiving the drug as an adjuvant to OIT. Further studies are needed to define the duration of such treatment.

7. Models of Dosing Schedules for CM and Egg OIT

(see Supplementary Material: Appendix 2).

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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