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REVIEW

Oral immunotherapy for food allergy: A Spanish guideline. Egg and milk immunotherapy Spanish guide (ITEMS GUIDE). Part 2: 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's milk and egg are the most frequent causes of food allergy in the first years of life. Treatments such as oral immunotherapy (OIT) have been investigated as an alternative to avoidance diets. No clinical practice guides on the management of OIT with milk and egg are currently available.
Objectives: To develop a clinical guide on OIT based on the available scientific evidence and the opinions of experts.
Methods: A review was made of studies published in the period between 1984 and June 2016, Doctoral Theses published in Spain, and summaries of communications at congresses (SEAIC, SEICAP, EAACI, AAAAI), with evaluation of the opinion consensus established by a group of experts pertaining to the scientific societies SEICAP and SEAIC.
Results: Recommendations have been 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 suffering adverse reactions.
Conclusions: A clinical practice guide is presented for the management of OIT with milk and egg, based on the opinion consensus of Spanish experts.

Maintenance phase of CM and EGG OIT

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

Food forms to be used

CM

The CM used during this phase is the same liquid pasteurized or UHT treated milk, with or without lactose, as that employed in the build-up phase. Other dairy products can be used, taking into account their respective protein concentrations, in order to ensure that the administered dose is equivalent to that afforded by liquid milk (see Part 1, Supplementary Table II. Protein contents of dairy products).

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, with consideration of a change in product.

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

If pasteurized or dehydrated egg-white is used during the build-up phase, regular intake of egg in its usual presentations (omelet, fried, scrambled, boiled, etc.) 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 must be warned that reactions may result from the intake of foods containing raw egg (e.g., sauces, creams, ice cream, etc.).[1,2] However, this strategy may suffice from the practical point of view, by making it possible to open the diet to all those foods that contain egg in its usual presentations (see Part 1, section D.4.2). If this option is chosen, periodic assessment of raw egg-white tolerance must be made. 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 to loss of sensitization or OIT failure

Conclusions:

- The CM used during this phase is liquid pasteurized or UHT treated 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 or equivalent allergen source (raw or cooked) used in the build-up phase.
- There are contradictory data 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 or rejection of egg must be assessed, with the decision of 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).

Dosing schedules

CM

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

- In patients that 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]
- Those patients that reach a dose of 200 ml during the build-up phase can consume milk or dairy products up to that amount or its equivalent, in addition to the scheduled maintenance dose. However, the patients are to be instructed not to consume these foods during the two hours before and after administration of the established maintenance dose. The aim of this measure is to avoid a high cumulative dose that could cause a reaction.

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

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

- When the patient is unable to reach a dose equivalent to a full serving of milk, maintenance should be carried out with the maximum dose reached during the build-up phase. The regular intake of lower doses than a full serving of milk contributes 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).

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 food?.

- Practically all studies of milk-OIT administer daily doses 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 (AR) have been observed on comparing a dosing schedules comprising daily doses versus a dosing schedules involving two weekly doses.[8]
- A decrease in dosing frequency, or a lack of adherence to therapy, could result in an increased number of AR.[9] If reducing the dosing frequency or temporarily suspending the treatment is intended, administration of the next dose should be made under medical supervision due to the risk of an allergic reaction.
- The physician in charge should be informed if the patient stops consuming milk for more than three consecutive days, in order to decide whether the next dose should be administered under adequate 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 is no evidence on the effect of fasting upon the safety of OIT with CM, most studies recommend avoiding administration of the dose under this condition, as doing so 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 conditions upon the OIT safety.[10]

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

Egg

What are the proposed doses in the maintenance phase of egg-OIT? Equivalent to a full serving dose or lower doses? In the case lower doses than a full serving of egg, should periodic challenge testing be considered for assessing 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 one egg – whether raw or cooked – the tolerance of doses equivalent to one egg should be checked by an oral food challenge.

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

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 food?.

- 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 three times a week.
- More frequent egg consumption during the maintenance phase favors the maintenance of desensitization.[14]

- Reduction of the egg dosing frequency during the maintenance phase should be carried out under medical supervision since allergic reactions may occur.[10,14]
- Discontinuous egg intake (less than three times a week) following the build-up phase may be a cause of allergic reactions during maintenance.[10]
- The physician in charge 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 concrete time of day is best for administering the egg dose, no ayuno vaya a realizar posteriormentom.
- Although there is no evidence on the effect of fasting upon the safety of OIT with egg, it is advisable to avoid fasting conditions, since an increased risk of allergic reactions might result.

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

Control and management of adverse reactions during oral immunotherapy

How should AR during the maintenance phase of OIT be controlled? What cofactors or triggering factors should be controlled or avoided during the OIT 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 guides.[15]

Reactions during this phase may be related to poor compliance or defective adherence to therapy[9,14,16] or to the action of cofactors. Physical activity following intake of the food[9,17–20] infectious processes[9,21] and uncontrolled asthma are risk factors for systemic reactions during the maintenance phase of OIT. Non-steroidal 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 association to cofactors.

Conclusions:

- The patients and their caregivers must be trained to adequately recognize and deal with the reactions that may develop during OIT (see Part 1, section ''Requirements referred to healthcare personnel, equipment and facilities: quality and safety standards'').
- Reactions during the maintenance phase of OIT may be related to poor compliance or defective adherence to therapy, or to the action of cofactors – though in some case no triggering factors are identified.
- Physical exercise following intake of the food, infectious processes, uncontrolled asthma, non-steroidal anti-inflammatory drugs, stress, menstruation and allergic rhinitis caused by aeroallergens have all been described as risk factors for systemic reactions during OIT.
- 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 adjustments to control such disorders is required, according to the needs of each patient.

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

What are the criteria for modifying the maintenance dose in the event of AR during the OIT maintenance phase?

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

1. Mild reactions: OIT can continue when the patient is asymptomatic, with repetition of the same dose the next day.
2. Moderate reactions: OIT can continue the next day, lowering the dose.
3. Severe reactions: The interruption of OIT or dose reduction should be considered.

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

Length of maintenance treatment

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

There are few studies on the long-term evolution of OIT, and no evidence has yet been gained regarding the minimum length of the maintenance phase.

In milk-OIT, the length 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 the patients.[6,21,24,25] The published data indicate that the long-term outcomes of OIT are heterogeneous: some patients lose desensitization status over 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 to favorable long-term outcomes: the serum baseline milk-sIgE; the appearance of gastrointestinal and respiratory symptoms during OIT; the threshold dose in challenge testing performed after three months of maintenance therapy; the amount of milk recommended each day; and the evolution of the milk skin prick tests in the course of the maintenance phase.

Two studies on egg-OIT evaluated the efficacy of the 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 in this phase, in place of the raw egg regularly administered during the build-up phase. In contrast, other studies have found up to 90% of the patients in the maintenance phase of OIT with egg to be able to consume the food without restrictions after 3–6 years of follow-up.[11]

Conclusions:

- No evidence has yet been gained regarding the required minimum length of the maintenance phase of OIT.
- Regarding the minimum length 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 AR in the last two years.

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

Assessment of permanent tolerance or ''sustained unresponsiveness''

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

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

In the study published by Staden et al., 75% of the responders (9/12 individuals) that successfully completed milk or egg-OIT exhibited permanent tolerance (2 months of avoidance diet) after 18–24 months.[10]

The studies of egg-OIT that have examined the achievement of permanent tolerance report incidences of permanent tolerance after OIT of between 28 and 75%, with very extreme maintenance periods of 3–36 months.[26–30] Aspects such as the length 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]

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 two reports the period was extended to 3–4 months.[34,35] However, it is not clear whether longer avoidance periods are able to guarantee tolerance of the food. In this regard, a study of peanut-OIT found that 50% of the patients (3/6 individuals) who passed a first challenge test after three months of avoidance diet following successful completion of OIT yielded a positive second challenge test after extending the avoidance period for another three months.[36]

Can specific IgE in the course of maintenance therapy act as marker of permanent tolerance?

High baseline sIgE at the OIT-start have been correlated to serious AR and low percentage of children that reach desensitization, in both the build-up phase and the maintenance phase[37] while low baseline egg and OVM-sIgE have been associated to the development of permanent tolerance.[38] The sIgE tend to decrease very slowly, remaining stable or higher on reaching the maximum tolerated amount of food, followed by a decrease in the course of the subsequent 12–18 months.[34,39]

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

The evolution of the titers of egg-sIgE in the course of OIT can be used as a predictor of permanent tolerance. In this regard, egg-sIgE against cutoff points have been identified – 7.1 kU/l for egg-white and 1.7 kU/l for ovomucoid – in determining the predictability of the challenge test outcome after OIT and an avoidance period of one month. The probability of a positive challenge test in the presence of titers above the cutoff point was found to be 90% and 73%, respectively.[33]

Conclusions:

- The results obtained to date referred to 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 length of the maintenance phase and the optimum food doses in order to secure permanent tolerance, with the identification of predictors to establish the best moment for assessing the achievement of this state though the evolution of the sIgE levels in the course of OIT might be useful in this regard. Evaluation of permanent tolerance development implies the need for a strict food exclusion diet during a period of 1–4 months, followed by oral food challenge under medical supervision. It is not clear whether avoidance periods of more than four months are able to influence permanent tolerance.
- Knowing whether a patient has reached permanent tolerance can have important practical consequences; the patient and family therefore should be informed about the advantages and inconveniences of performing this evaluation.

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

Long-term follow-up: required period of time

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 referred to the length of treatment, few studies are available on the long-term outcome of OIT, and the follow-up periods moreover range between 1 and 6 years.[1,2,6,11,36,38,45] Over 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]

AR 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 the 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 four weeks. The achievement of permanent tolerance status 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).

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?

The patients must be evaluated periodically after OIT. In this regard, most studies conduct follow-up every 6 months during the first 18 months[30] or first three years. In clinical practice, most authors perform controls with skin prick tests and the 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 control the regular food intake and acceptance of the recommended food doses.

The evolution of sIgE levels may be useful for assessing progression toward permanent tolerance.[33]

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

Conclusions:

- During the follow-up of patients subjected to OIT, clinical assessment is required one 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 the 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 to CM and/or egg are indicated throughout the follow-up period.

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

Special dosing schedules in milk and egg-OIT

Identification of patients at risk of suffering AR and OIT failure

What clinical criteria allow the identification of patients at risk of suffering AR and OIT failure?

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]

Coexistence with asthma. In anaphylaxis, the coexistence of asthma is a risk factor associated to 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 AR during treatment, particularly in cases of moderate-severe asthma.[10,17,22,31,46,48–52]

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

On the other hand, the high prevalence of respiratory allergic disease in adolescents with food allergy – asthma in these cases being more severe[9,24,31] and in some cases poorly controlled because of the previously mentioned factors and frequent intense physical activity – are important cofactors in the appearance of AR.

What biological criteria allow the identification of patients at risk of suffering AR and failure with OIT?

Magnitude of the result of baseline skin prick testing. The results of the studies on milk-OIT indicate the following:

- Skin prick testing with CM diluted to 1/1000 and yielding >5 mm (odds ratio [OR] 8.3; 95%CI 1.9–35.5) constitutes a risk factor for torpid patient evolution.[53]
- The association of two or three of the following factors: skin prick test results with CM >9 mm, IgE levels >50 kU/l, and grade 2, 3 and 4 reactions to challenge testing, imply a high risk of recurrent AR during OIT.[17]

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

Baseline serum specific IgE levels. The results of milk-OIT studies indicate:

- The baseline milk-IgE levels are greater in children in which treatment fails than in those in which desensitization is achieved ($p < 0.05$).[38]
- Patients with baseline milk-sIgE >50 kU/l suffered frequent reactions more severe, less predictable and more persistent, or resulted in OIT failure.[6]
- Patients with milk-sIgE levels >75 kU/l have a poorer long term prognosis in terms of treatment failure or reductions in tolerated milk dose.[8]
- Milk and casein-sIgE levels $\geq$17.5 kU/l increased the risk of a torpid OIT, independently of patient age, sex or comorbidity as asthma.[53]
- The baseline differences in IgE recognition to milk linear peptides could constitute a risk marker for AR and OIT failure.[40,54]

The results of egg-OIT studies indicate:

- OVM-sIgE levels <8.85 kU/l are predictive of OIT success. Higher titers are associated to a 95% probability of more frequent AR that moreover persist over time, and of early withdrawal.[10]

Symptoms-triggering dose in milk and egg challenge tests before OIT. Patients with poorer OIT outcomes are those yielding positive challenge test results with lower doses, though the doses that may be regarded as ''low'' have not been established to date.[43] The reported doses related to AR and failure of milk-OIT range from 1 to 2.5 ml.[17,18,22] Regard to egg-OIT, the reported dose is approximately 1 ml of raw egg-white[2,14,47] and a quarter of cooked egg-white.[10]

***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 cutoff points have been established, we recommend reference levels of 17.5 kU/l for casein and 8.8 kU/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 cutoff 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 such patients, in view of the circumstances that characterize this stage in life. (Level of evidence V. Grade of recommendation D: expert opinion).

What to do to improve safety in patients at risk

Would it be advisable to apply OIT with lesser dose increments and greater prolongation over time?

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 contribute to increase the threshold and represent an alternative dosing schedule in these patients at risk.

Sublingual immunotherapy (SLIT) with CM or egg

Is it effective and safe?. Placebo-controlled studies involving 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 of SLIT versus OIT, though with comparatively lower efficacy, or without differences versus placebo, as has been seen in a study with peanut.[59] No studies has been published on egg SLIT.

Should the SLIT dose be spited out or swallowed?. SLIT with food uses the same technique as SLIT with allergens.

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

When to use SLIT: as pre-treatment or co-treatment with OIT?. It has been suggested that pre-treatment with SLIT followed by OIT could benefit the safety and efficacy profile of OIT.[67] One study examined OIT and pre-cotreatment with peanut-SLIT. This strategy was seen to afford substantial protection against AR in comparison with OIT alone.[61]

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] though doses of up to 32 mg (1 ml) with good tolerance.[63] The maximum tolerable volume appears to be 1 ml, the maximum amount used in the described studies.

Treatment with omalizumab during OIT

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

What doses and frequencies of administration should be used?. OMZ dosing and administration interval proposed are calculated based in total IgE levels and patient weight according to the Summary of Product Characteristics for the treatment of severe allergic asthma.[71,73,74,76–78,80] If serum IgE levels exceed 700 kU/l, the dose is calculated by applying the formula 0.016 mg/kg/IgE (kU/l)[76] with a maximum dose of 600 mg every two weeks.[77]

What OMZ administration schedule should be used?. Most studies make use of a pre-treatment dosing schedules, administering OMZ before starting OIT, during a variable time period of 4–18 weeks.[72–80]

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

The use of the drug is therefore not limited only to pre- and co-treatment with OIT. The introduction of OMZ at any time of OIT has been evaluated as rescue therapy.[78]

Regard the time to stopping OMZ after having reached the maximum OIT dose, the data vary considerably (between 1 and 19 months)[74,76,77,80,82] though most studies discontinue the drug between 1 and 2 months after concluding OIT.[74,76,82]

Does OMZ suspension after OIT increase the risk of serious AR?. Immediate tolerance after OMZ suspension is variable. In one study, 100% of the patients that 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 intake of the food appeared to continue with no symptoms or only mild and tolerable symptoms following suspension.[73,74,82] However, a proportion of the patients (33–60%) suffered relapse with a drop in the clinical responsiveness threshold 2–4 months after suspending OMZ.[80,83] The difference may lie in the degree of clinical responsiveness and sensitization of the patients.

Furthermore, those studies that prolong the length of follow-up have documented a relapse in terms of symptoms reappearance with the food over time without OMZ. Between 6 and 8 months after suspending OMZ, reactions appear in up to 50% of the patients. Most of these reactions are mild, but some patients suffer severe reactions requiring epinephrine.[76] All this suggests needs to increase the length of maintenance treatment with OMZ, and the advisability of conducting further studies to help define the adequate length of such therapy.

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

Therapeutic strategies to increase safety. **Conclusions:**

- Reduction of the dose increments

The dose increments should be optimized, reducing them to minimize the possible adverse effect of the treatment and increase efficacy.

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

- Pre-cotreatment with SLIT

Sublingual immunotherapy is accepted as a potential treatment for favoring the acquisition of desensitization to some foods. Benefits in terms of both immunological parameters and efficacy have been documented, though to a lower degree than with OIT. In contrast, SLIT is associated to 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 as a coadjuvant to OIT. (Level of evidence V. Grade of recommendation D: expert opinion).

The length of pre-treatment with SLIT should be at least 6 weeks before the start of OIT, though it subsequently may be maintained as co-treatment with OIT. (Level of evidence V. Grade of recommendation D: expert opinion).

The recommendable 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 that are highly sensitized and/or present clinical manifestations of anaphylaxis. (Level of evidence V. Grade of recommendation D: expert opinion).

- OMZ as an adjunct to OIT

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

The recommendation is to use the OMZ 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/l) can be applied, with a maximum dose of 600 mg every two weeks. (Level of evidence V. Grade of recommendation D: expert opinion).

OMZ should begin as pre-treatment during no less than four weeks before the start of OIT – the recommendation being 9 weeks before the start of OIT. (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 OMZ in patients receiving the drug as adjuvant to OIT. Further studies are needed in order to help define the length of such treatment.

Models of dosing schedules for CM and egg-OIT

see Supplementary Materials: Appendix 2.

Ethical disclosures

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Conflict of interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.aller.2017.05.002.

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