Comprehensive Review of Current Knowledge on Egg Oral Immunotherapy

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Abstract

Oral immunotherapy (OIT) is an attractive strategy for active treatment of IgE-mediated food allergy. Multiple egg OIT studies have been published to date, but many are uncontrolled. Furthermore, interpretation of the results is difficult because of significant heterogeneity in design, aims, and population. Most studies have demonstrated the potential of egg OIT to induce desensitization, albeit to different extents (0%-100% of patients). However, few studies have explored the capacity of OIT to maintain tolerance, that is, enabling the patient to continue consuming egg after suspension of therapy. Nowadays, 28% to 75% of patients maintain tolerance after 1 to 3 months of their elimination diet. Adverse effects are the main drawback of this treatment, which is still not recommended in routine practice. Adverse reactions are not reported homogeneously, with the result that it is difficult to properly assess outcomes. The overall impression is that adverse reactions affect most patients and tend to be frequent, although of mild to moderate severity. Nevertheless, severe events such as anaphylaxis or eosinophilic esophagitis may also occur. Immunological changes resulting from egg OIT, for example, the decrease in the size of the skin prick test wheal and the levels of egg white sIgE and a significant early increase in egg white sIgG4, have been reported. Several areas of egg OIT remain unclear, including patient selection, materials used, dosing schedule, treatment duration, long-term maintained effectiveness, requirements for implementation in clinical practice, influence on quality of life, and cost-effectiveness of treatment.
In this review, we provide an in-depth examination of methodological differences between studies in order to understand the diversity in the efficacy and safety results of the procedures used in egg OIT.

Key words: Oral Immunotherapy. Egg desensitization. Egg tolerance. Food-immunotherapy. Egg allergy. Adverse events. Adverse reactions. Treatment of food allergy

Resumen

La inmunoterapia oral (ITO) supone una atractiva estrategia como tratamiento activo de la alergia a los alimentos mediada por IgE. Se han publicado múltiples estudios sobre ITO con huevo, sin embargo, la interpretación y comparación de los resultados es difícil debido a la heterogeneidad en el diseño, el objetivo de los estudios y la población incluida. La mayoría de estudios han demostrado la capacidad de la ITO para inducir desensibilización a huevo en diferentes grados (0-100% de los pacientes). Sin embargo, pocos trabajos han explorado la capacidad de la ITO para inducir tolerancia mantenida lo que implica la tolerancia a huevo a pesar de la suspensión de su ingestión regular. En los estudios publicados hasta la actualidad, la tolerancia a huevo mantenida tras la ITO en pacientes alérgicos varía entre el 28 y el 75%. Las reacciones adversas representan el principal inconveniente de este tratamiento, es la causa principal del fracaso del tratamiento y de que aún no se recomiende en la práctica habitual. La manera de notificar las reacciones adversas durante la ITO con huevo es muy diferente en cada estudio, lo que dificulta la valoración de la seguridad del procedimiento. La impresión general es que las reacciones adversas afectan a un porcentaje significativo de pacientes y tienden a ser frecuentes, pero su gravedad suele ser de leve a moderada. Sin embargo, también pueden producirse acontecimientos graves como anafilaxia o esofagitis eosinofílica. Los investigadores coinciden en que existen cambios inmunológicos durante la ITO con huevo como la disminución en el tamaño de la prueba cutánea y los niveles de IgE a clara de huevo y un aumento significativo de la IgG4 a clara de huevo. Aún existen muchos aspectos de la ITO con huevo que deben ser mejor definidos, como la selección de pacientes, la fuente alergénica utilizada, la pauta de administración, la duración del tratamiento, la eficacia mantenida a largo plazo, la influencia en la calidad de vida o el coste-efectividad del tratamiento y establecer las bases para su aplicación en la práctica clínica.
El objetivo de esta revisión es analizar las diferencias metodológicas entre los estudios publicados, con el fin de comprender la diversidad en los resultados y vislumbrar con los datos disponibles, la eficacia y la seguridad de la ITO con huevo.

Palabras clave: Inmunoterapia oral. Desensibilización a huevo. Inducción de tolerancia a huevo. Inmunoterapia con alimentos. Alergia a huevo. Reacciones adversas. Eventos adversos. Tratamiento de alergia a alimentos.

Introduction

Food allergy is a relevant health concern, and its prevalence has increased over the past 10 years [1]. Egg allergy is the second most frequent food allergy in children worldwide [2-3] and the main cause of food allergy in children under 14 years of age in Spain [4]. Most adverse reactions (ARs) to egg are IgE-mediated, with symptoms ranging from oropharyngeal reactions or skin reactions to life-threatening anaphylaxis [5]. Thirty-four percent of Spanish patients outgrow egg allergy by the age of 5 years [6]. However, American studies show that 12%-53% of patients outgrow egg allergy by the age of 5-6 years [7-8].

Strict avoidance of egg protein intake is the only standard of care, although it is hampered owing to the extensive use of egg protein in foodstuffs, which significantly impairs quality of life [9].

It is therefore vital to identify curative approaches for food allergy to eliminate the risk of ARs due to accidental ingestion or contact [10]. The several allergen-specific strategies being developed for food allergies include oral, sublingual, epicutaneous, and subcutaneous administration of small increasing amounts of native or modified allergens to induce immune tolerance. To our knowledge, subcutaneous and sublingual egg immunotherapy has not been investigated [11], and epicutaneous egg immunotherapy studies are still in the preclinical phase [12]. Oral immunotherapy (OIT) was first described in 1908 in a patient with egg anaphylaxis [13], but it was not until almost a century later that it started to be used for the treatment of food allergy [14]. It has been studied for more than 3 decades, especially in the last 8 years, and seems to be the most promising approach among emerging therapies for egg allergy.

Food OIT involves regular oral administration of allergen in increasing amounts to induce desensitization in a relatively short time frame. Current egg OIT protocols typically include 2 phases (Figure). The first is the induction phase or dose increase phase, performed under observation, which often includes an initial phase with several doses of allergen given rapidly and a build-up phase, during which the dose is increased every day or every 1 to 2 weeks until a target dose is reached. The second phase is the maintenance phase, during which the food-allergic patient takes the food regularly at home and becomes desensitized.

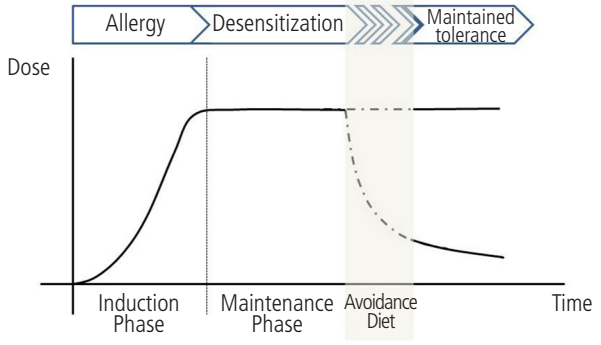

Figure. Schematic overview of the different phases and goals in OIT.

The ultimate aim of egg OIT is to establish oral tolerance to egg allergens through long-term curative treatment of egg allergy. Nevertheless, successful egg OIT can achieve 2 states: desensitization and maintained tolerance [15] (also known as sustained unresponsiveness [16], permanent tolerance [17], and clinical immune tolerance [18]). Desensitization refers to the ability to ingest a food without reaction while continuing to take regular doses of that food. Hence, the individual remains allergic, and ingestion of the food after a period of elimination (discontinuation of immunotherapy) could result in an acute allergic reaction. In contrast, maintained tolerance is the ability to tolerate a food after a period of food avoidance and has to be assessed by performing an oral food challenge (OFC) after discontinuing ingestion of the allergen for a period of at least 4 weeks [15-21].

The state of desensitization is mediated by changes in effector cells (mast cells and basophils), with no deep modulation of underlying pathogenic immune mechanisms. The acquisition of maintained tolerance is believed to reflect reprogramming of the immune response to the allergen through involvement of regulatory T cells or other T-cell subsets and/or allergen-specific anergy and clonal deletion. Maintained tolerance is expected to persist for at least some months after therapy for food allergy has been discontinued [22].

Although this treatment can be administered at any age, even during the first years of life [23], most studies tend to be performed in patients with less chance of outgrowing their egg allergy. Patients with more severe allergic reactions due to egg or with higher serum egg-specific IgE (sIgE) levels would benefit more from successful OIT. At the same time, such patients are also at higher risk of ARs during treatment [24].

Assessment and comparison of the efficacy and safety of protocols is complicated owing to the high degree of variability between them in terms of inclusion criteria (eg, age, egg-sIgE levels, asthma, previous severe and anaphylactic reactions, with/without baseline OFC), egg material used, dosage, target dose, duration of the induction phase, time in the maintenance phase, assessment and recording of ARs, and cofactors. When considering efficacy, it is necessary to bear in mind the differences in the objectives of the studies in terms of desensitization and/or maintained tolerance, as well as the risk-benefit ratio for each patient.

In this review, we examine the methodology, efficacy, and safety of the different procedures used in egg OIT.

Materials Used in Egg OIT

The extracts used in egg OIT can be modified or natural products (Table 1). In modified products, allergenicity can be similar to that of the natural form [25,26] or decreased. The products are generally obtained through thermal procedures [27]. The allergen source used during the maintenance phase can be the same as that used during the induction phase, or it can be replaced by undercooked fresh egg (omelette, scrambled egg, fried egg) or hard-boiled egg. Whole raw eggs have been used at the end of the induction phase and for maintenance in several studies [28-30]. In most studies, the natural source has been modified, as is the case with pasteurized whole egg [31], pasteurized raw egg white [24,32,33],

lyophilized egg white [17], dehydrated whole egg [34], and dehydrated egg white [15,16,19-21,35,36]. This has facilitated handling and storage, dose control, and control of bacterial contamination. In vivo and in vitro allergen equivalence has been demonstrated between raw and pasteurized egg white [25] and raw and dehydrated egg white [26].

Equivalence between each of these products and natural egg in terms of protein content depends on the egg product and the size of the reference egg, since the weight of an egg may vary from less than 53 g for an S-sized egg to over 73 g for an XXL-sized egg. The protein content of a whole egg is about 12.6% of its weight. In addition, hard-boiled egg is less

Table 1. Types of Egg Products and Their Equivalences According to the Authors

Extract	Equivalence to Natural Source According to Authors	Percent Protein in the Product (Weight)	Production System	References
Natural whole egg[a]	100%	13% 1 medium-size egg (60 g) = 7 g of proteins	NN	*Raw:* Dello Iacono et al [28] Meglio et al [29] Patriarca et al [30] *Cooked:* Itoh et al [36] García Rodríguez et al [33] *Boiled:* Morisset et al [38]
Natural egg white	70% of the edible weight of an egg	10.2%	NN	Not used
Natural egg yolk	30% of the edible weight of an egg	16.1%	NN	Not used
Liquid pasteurized whole egg	50 mL = 1 egg	11.5%	Egg heated to 64.5°C for 150 seconds	Ojeda et al [31]
Liquid pasteurized egg white	1 mL = 0.083 g of EW protein	10.7%	NR	Vazquez-Ortiz et al [24] Tortajada Girbés et al [32]
	30 mL = 1 EW	NR	EW heated to 57°C for 4.25 min	Garcia-Rodríguez et al [33][c]
Lyophilized whole egg	7 g =5.6 g of protein = 1 egg	80%	Freeze-dried egg: freezing the egg and then reducing the surrounding pressure to allow the frozen water in the egg to sublimate directly from the solid phase to the gas phase, leaving a solid material[b]	Staden et al [17]
Dehydrated whole egg	10 g = 1 egg	NR	NR	Fuentes-Aparicio et al [34]
Dehydrated egg white	1 g = 8 g EW	NR	NR	Itoh et al [36][c]
	3.6 g = 2.8 g EW protein = 1 EW	78%	Raw EW is pasteurized (heated to 59°C for 6 min), and the pH is then adjusted to 6.5-7.5 by addition of citric acid. Oxidizing glucose, catalase, and hydrogen peroxide are then added to remove glucose and prevent the Maillard reaction. Finally, EW is passed through a spray tower, where it is dried with hot air at 80°C for 1 minute	Escudero et al [21] Ruiz García et al [35]
	2 g = 1.6 g EW protein	80%	NR	Buchanan et al [20] Vickery et al [19] Burks et al [16]
	4 g = 1 EW	NR	An egg was pasteurized and then passed through a spray tower where it was dried	Caminiti et al [15]

Abbreviations: EW, egg white; NN, not needed; NR, not reported.
[a]The amount of protein varies according to the weight of the egg, which can range from less than 53 g for an S-sized egg to more than 73 g for an XXL-sized egg.
[b]Data not provided by the authors; explanation included for the sake of comprehension.
[c]At the first stages of the induction phase.

allergenic than raw egg owing to the thermolability of the main egg allergen proteins, except for ovomucoid [27,37]. In fact, protocols that proved efficacy in desensitizing egg-allergic patients to hard-boiled egg were less efficacious at inducing desensitization to raw products [38]. The aim of using hard-boiled egg is to partially normalize patient diet [38].

In mixed protocols, up to about 1000 mg of raw egg was used during the first doses, followed by the equivalent of 1 cooked egg [36].

Comparison of equivalence between the doses administered during egg OIT in different protocols is extremely difficult, since their equivalence as regards raw egg white or egg is not always included (Table 1). This problem would be minimized if all protocols expressed doses of egg protein in milligrams.

Induction Phase: Desensitization Protocols and Efficacy

The purpose of the induction phase is to reach a targeted dose of egg that will be ingested periodically during the maintenance phase. Several methodological differences should be taken into account: the target dose can be at least 1 raw egg (a whole raw egg or a raw egg white), a dose of less than 1 serving of egg, or egg presented in a diminished allergenic form (heated egg). The last 2 options are aimed first at protecting the patient from accidental reactions and second at achieving tolerance to higher doses after a maintenance phase, which is usually confirmed through an OFC. Different dose escalation schemes, amounts of egg, and material have been reported. Table 2 shows the characteristics of the studies and published protocols of egg OIT. In controlled studies, egg-allergic children following an egg avoidance diet were recruited as a control group, except in 2 placebo-controlled studies [15,16]. Analysis of protocols should make a clear distinction between those using cooked egg and those using raw egg or equivalent products.

The most relevant studies whose objective was desensitization to cooked egg include those published by Itoh et al [36] (scrambled egg) and García-Rodríguez et al [33] (omelette), neither of which includes a control group. Egg allergy was confirmed by performing a baseline double-blind, placebo-controlled food challenge (DBPCFC) in one case [36] and an egg open OFC (in 52% of patients) in the other [33]. OIT in these studies was administered as a rush schedule, with several daily dose increases. Itoh et al reported 6 patients with previous anaphylaxis and a mean age of 9.7 years, history of asthma, and undeclared baseline egg sIgE. García-Rodríguez et al included 23 patients with a mean age of 8.1 years and a mean egg white sIgE of 9.87 kU_A/L; 65% were asthmatic. In the study by Itoh et al, up to 1000 mg of dehydrated egg white was used first, followed by cooked egg up to the end of the induction phase. All patients were able to tolerate the ingestion of 1 scrambled egg in a mean induction phase of 12 days. García-Rodríguez et al used up to 8 mL of pasteurized egg white, which is equivalent to 1060 mg of powdered egg white and, on the last day, 1060 mg of raw pasteurized egg white plus a whole cooked egg (omelette). This protocol was successful in 86.9% of patients over a median of 11 days in the induction phase. However, in their home-based, randomized controlled study, Morisset et al [38] used hard-boiled egg at a slower dosing rate (4 months) and assessed the patients with an open OFC (up to 7 g of raw egg white) before and after treatment. They administered increasing amounts of hard-boiled egg from the first doses up to 4 g of egg yolk plus 4 g of egg white. In the third month, flan and cream desserts were included as maximum induction phase doses. This study included patients (51 active and 39 control) who tolerated at least 965 mg of raw egg white in the baseline OFC. The mean age was 3.6 years, and the mean egg white sIgE was 3.8 kU_A/L. The percentage of asthmatics was not reported. After 6 months of treatment, 51.4% of control patients and 69.4% of active patients passed OFC with 7 g of raw egg white. This nonsignificant difference in treatment efficacy between the active and the control group can be explained by the high threshold dose during the baseline OFC in selected patients, the egg product used, the low target doses chosen for this treatment, the low baseline levels of egg white sIgE, and/or the age of the population, which was lower than that reported in other studies, indicating that patients were more likely to overcome egg allergy spontaneously.

Many studies and schemes use different forms of raw egg. In order to facilitate analysis, they are classified arbitrarily according to the duration of the induction phase as fast (<3 months), intermediate (3-6 months), and slow (>6 months).

Escudero et al [21] took a median of 32.5 days to reach the target dose, Ojeda et al [31] 43 days, Ruiz-García et al [35] a mean of 49 days, Buchanan et al [20] 66 days, and Fuentes-Aparicio et al [34] 70 days. Therefore, all are considered fast protocols. Escudero et al included 61 patients with egg allergy confirmed through a baseline DBPCFC (mean age of 8.7 years, 41% asthmatic patients), who were randomized to active treatment and control treatment at a 1:1 ratio. Median baseline egg white sIgE was 6.4 kU_A/L for patients receiving active treatment and 2.2 kU_A/L for control patients. The induction phase comprised 9 doses of dehydrated egg white with 1 escalation per week. Ninety-three percent of active patients were desensitized to a dose equivalent to 1 raw egg white in a median of 32.5 days. Three percent of control patients tolerated egg spontaneously after a 4-month avoidance diet, confirmed by DBPCFC. Ojeda et al used a home protocol with small daily increases (1.2-1.5–fold) of pasteurized whole egg in 31 active and 3 nonrandomized egg-allergic control patients (mean age of 9.6 years and mean ovomucoid sIgE of 9.92 kU_A/L). Eighty percent of patients in the active group were desensitized, although there is no information on the control group. In their noncontrolled study, Ruiz-García et al desensitized 73.3% of the 19 egg-allergic patients included (mean age, 7.9 years [16 children], 28.3 years [3 adults]; mean ovomucoid sIgE, 2.4 kU_A/L), who were able to tolerate a whole dehydrated egg white. Buchanan et al provide no clear information on the mean time to the target desensitization dose (300 mg of protein). However, analysis of the methodology and results shows that the induction phase lasts around 66 days. All of the 7 patients included (mean egg sIgE of 23.75 kU_A/L; 43% asthmatic) completed the induction phase successfully, and 57% tolerated 8 g of egg protein during the DBPCFC plus 6.7 g of scrambled egg in an OFC 2 years later. The protocol, which had no control group, consisted of a rush phase on the

first day, followed by a biweekly updosing phase with increases in fixed doses. Fuentes-Aparicio et al included 72 patients randomized to an active treatment group (n=40, mean age of 8.7 years and mean ovomucoid sIgE of 7.98 kU_A/L; 70% asthmatic patients) and a control group (n=32, mean age 9.4 years, mean ovomucoid sIgE of 7.23 kU_A/L). Patients in the active group completed a protocol with dehydrated whole egg, which consisted of a rush phase during the first day, followed by a weekly updosing phase. Desensitization was achieved in 92.5% of patients up to the equivalent of 10 g of dehydrated whole egg. Six months after the induction phase, 54% of the desensitized patients tolerated 1 raw egg white in an OFC, that is, 50% of all the included patients in the active treatment group. At 12 months from baseline, 21.8% of control patients overcame their egg allergy spontaneously.

Caminiti et al [15], Vázquez-Ortiz et al [24], Vickery et al [19], and Dello Iacono et al [28] used intermediate protocols (3-6 months), with approximate mean times to reach the target dose of 112, 135, 174, and 176 days, respectively. Caminiti et al conducted a study with 17 active and 14 control patients (mean age of 6 years, mean egg-sIgE of 36.6 kU_A/L) with dehydrated egg white up to a maximum of 4 g. Ninety-four percent were desensitized. The dose was increased once per week by doubling the previous dose. Vázquez-Ortiz et al included 50 active and 32 control patients who were not randomized (mean age of 8.3 years; mean egg white sIgE of 6.44 kU_A/L; 64% asthmatic patients). The authors used pasteurized egg white with a rush phase during the first 2 days, followed by weekly updosing to the equivalent of 1 raw egg. Fifty-four percent of the active group tolerated 60 g of raw egg at 12 months, while 15.6% of control patients overcame egg allergy spontaneously. Early discontinuation or ongoing reactions during egg OIT was associated with underlying asthma, higher baseline specific IgE (ovomucoid sIgE $\geq$8.85 kU_A/L), and a lower threshold in the DBPCFC.

Vickery et al [19] included 8 patients (mean age of 5 years; mean egg white sIgE of 12.5 kU_A/L; 37.5% asthmatic patients) who were treated with several doses during the first initial escalation day and biweekly updosing to 300 mg of egg white protein in the form of dehydrated egg white. Egg white sIgE was subsequently recorded every 4 months, and, depending on the results, patients with <2 kU_A/L underwent OFC up to 3900 mg of dehydrated egg white. Patients with an egg white sIgE >2 kU_A/L qualified for updosing to 600 mg, which was maintained for the following 4 months, up to a maximum maintenance dose of 3600 mg at the subsequent 4-month reassessments. Seventy-five percent of the patients were desensitized with this protocol. Dello Iacono et al [28], confirmed egg allergy in a screening DBPCFC in 20 children, who were randomized 1:1 to an active group (mean age of 6.6 years; mean egg white sIgE of 23.3 kU_A/L; 40% asthmatic patients) and a control group (mean age of 8.6 years; mean egg white sIgE of 19.1 kU_A/L; 40% asthmatic). The dosage consisted of daily 1.1-fold or 1.2-fold increases at home and a double dose once a month in the hospital. The objective of this protocol was desensitization to the equivalent of 1 raw egg, although none of the patients in the active group achieved this goal. Ninety percent (9/10) of patients in the active group were partially desensitized and tolerated 10 mL to 40 mL of raw egg.

Meglio et al [29], Staden et al [17], and Burks et al [16] used protocols with an induction phase of over 6 months, with periods of desensitization ranging from 215 days (7 months) to a maximum of 300 days (10 months, although the exact time is not specified). Meglio et al included 20 allergic patients randomized 1:1 to an active treatment group (mean age of 8.4 years; median ovomucoid sIgE of 6.8 kU_A/L) or a control group (mean age of 9 years; median ovomucoid sIgE of 4.9 kU_A/L). Most were assessed using DBPCFC before their inclusion in the study, and 80% were desensitized to 25 mL of raw egg. The daily increased dosage at home was calculated using a mathematical formula (9% increase during the first 80 days, 3.9% from then onwards). Staden et al randomized egg-allergic patients to an active treatment group (11 patients) and a control group (10 patients). Active group patients underwent a home induction phase–based protocol with lyophilized egg (2.8 g of protein, ie, half an egg). The exact percentage of success of egg OIT was not reported because the authors made a joint assessment of patients with egg OIT and milk OIT, but approximately 64% of patients in active group were totally or partially desensitized. The control group was only assessed at the end of the study period, and 35% of its patients spontaneously outgrew their allergy

Burks et al [16] carried out a randomized, double-blind, placebo-controlled study with no baseline OFC using a dose that enabled them to reach a maximum of 1.6 g of egg white protein. The trial included 55 patients (mean age of 7 years), 40 active patients (median egg-sIgE of 10.3 kU_A/L), and 15 patients receiving a placebo (median egg sIgE of 25.7 kU_A/L). The process started with an escalation on the first day, followed by a biweekly build-up phase of +25%. At 10 months, 55% (22/40) of active patients passed a DBPCFC with 5 g of egg white protein and 30 (75%) tolerated 10 g in a DBPCFC at 22 months of the maintenance phase. None of the 15 patients in the placebo group tolerated the DBPCFC with 5 g of dehydrated egg white at 10 months or with 10 mg at 22 months (only 1 patient was eligible for this food challenge).

We found only 1 systematic review of the literature [11] comprising studies on egg OIT: 4 randomized controlled trials using an extract with preserved allergenic capacity [16,28,29,34] were selected for analysis. The trials included a total of 167 children aged between 4 and 15 years (100 active, 67 control patients). By the end of treatment, 39% of active patients could tolerate 1 serving of egg (1 egg) compared with 11.9% of control patients (RR, 3.39; 95%CI, 1.74-6.62). Seventy-nine percent of patients receiving egg OIT could tolerate a partial serving of egg (1 g to 7.5 g [RR, 5.73; 95%CI, 3.13-10.50]). The difference in success rates between studies is extreme and may be due to factors such as differences in definitions of treatment efficacy. Thus, the frequency of desensitization in these studies was as follows: 92.5% for Fuentes-Aparicio et al [34], 80% for Meglio et al [29], 55% at 10 months of treatment for Burks et al [16], and 0% for Dello Iacono et al [28].

The data reported reveal relevant methodological concerns, such as the low number of patients included in randomized controlled trials, the marked variability between protocols, the time when response to treatment is assessed, and the varying definitions of success, all of which hamper comparisons between protocols. Efficacy for desensitization ranges from 0% [28] to 100% [20,36]. In addition to the aforementioned

Table 2. Summary of Studies Egg on Oral Immunotherapy

	No. of Patients Mean/Median Age, y (Range)	Study Design	Mean/Median (Range) sIgE, kU_A/L	Asthmatics, %	Duration of IP		Maximum Dose in IP	Efficacy of Desensitization	Maintenance Phase: Dose and Period of Follow-up	Maintained Tolerance: (N) Avoidance Diet Time and Efficacy (Passed OFC)[a]
					Programmed Mean	Final Mean (Range)				
Patriarca et al, 2007 [30]	Ac: 17 9.2 (4-16)	Not randomized, controlled	NR	NR	168 d	5-8 mo	50 mL of raw egg	Total: 12 (70.6%) Partial: 2 (11.8%)	1 egg at least 2 or 3 times/wk (form not specified) Period not reported	NR
Staden et al, 2007 [17]	Ac: 11 egg + 14 milk Con: 20 (milk + egg) 2.5 (0.6-12.9)	Randomized controlled, home-based protocol	NR	NR	67 d	7 mo (70 d-12 mo) 2/11: 28 and 48 mo	2.8 g of egg protein	Total: 12/25 (48%) Partial 4/25 (16%) Failure 9/25 (36%)	Minimum of 1.6 g/d of egg protein plus deliberate intake Mean 9 mo (7-15 months)	(16 egg+milk) 2 mo Ac: (egg+milk): 9/25 (36%) Con: 7/20 (35%)
Morisset et al, 2007 [38]	Ac: 49 Con: 39 3.6 (1-8)	Randomized Controlled Home-based protocol	EW-sIgE: 3.8	NR	3 mo	3 mo	Regular intake of egg containing cookies, flans, and creams	Tolerated 7 g of raw EW in SBPCFC after 6 mo of treatment: Ac: 34/49 (69.4%) Con: 18/35 (51.4%)	Dose not clearly stated (cookies and flans) 6 mo	NR
Buchanan et al, 2007 [20]	Ac: 7 3.7 (1.2-7)	Not randomized, not controlled	Egg-sIgE: 23.7 (16.9-64.4)	3 (43%)	NR	66 d	0.3 g of DEW	Total: 7 (100%) 24 mo: 4/7 (57%) tolerated 8 g of egg protein in DBPCFC. + 6.7 g of scrambled egg openly)	0.3 g /d 24 mo	(4) 3-4 mo 2/7 (28,5%)
Vickery et al, 2010 [19]	Ac: 8 5 (3–13)	Not randomized, not controlled	EW-sIgE: 12.5	3 (37.5%)	4 mo	Median, 174 d (IQR, 52 d)	0.3 g, but if EW-IgE remained >2 kU_A/L, IP continued up to 3.6 g	Total: 6/8 (75%) reach 0.3 g of dehydrated EW At 4 mo: 5/8 (62.5%) tolerated 3.9 g in OFC	Median dose of 2.4 g/d (0.3-3.6 mg) Mean 33.8 mo (SD, 14.5 m)	(6) 1 mo 6/8 (75%)
Itoh et al, 2010 [36]	Ac: 6 9.7 (7-12)	Not randomized, not controlled	NR	6 (100%)	NR	Median, 12 d (9-18 d)	1 scrambled egg (60 g)	Total: 6/6 (100%)	≥1 cooked egg twice/wk 16-21 mo 3/6 (50%) did not tolerate 1 g of DEW after 9 mo of MP	NR
García-Rodriguez et al, 2011 [33]	Ac: 23 8.1 (5-17)	Not randomized, not controlled	EW-sIgE: 9.8 (0-100)	15 (65.2%)	5 d	11 d 2/23: 60 and 80 d	8 mL of pasteurized egg white + 1 cooked egg	Total: 20/23 (86.9%) 2/23 (8.7%): success in 60 and 80 d	1 cooked egg/24 h first 3 mo; 1 cooked egg/48 h for 3-6 mo, after 6 mo 1/72 h 6 mo	NR
Tortajada-Girbés et al, 2012 [32]	Ac: 19 7 (3-14)	Not randomized, not controlled	NR	8 (42%) (rhinitis or asthma)	16 wk	NR	30 g of egg	Total: 17/19 (89.5%)	NR	NR
Burks et al, 2012 [16]	Ac: 40 Con:15 (10 mo placebo) 7 (5-11)	Randomized, placebo controlled	Ac: Egg-sIgE: 10.3 (3.7-231)	NR	224 d	NR	EW protein. Maximum: 1.6 g Minimum: 0.306 g	10 mo: tolerated 5 g in DBPCFC Ac: 22/40 (55%) Con: 0/15 (0%) 22 mo: tolerated 10 g in DBPCFC Ac: 30/40 (75%) Con: 0/1 (0%)	Up to 2 g DWE/d (EW protein; maximum 1.6 g, minimum 0.3 g) 24 mo	(29) 4-6 wk 11/40 (28%)

	No. of Patients Mean/Median Age, y (Range)	Study Design	Mean/Median (Range) sIgE, kU_A/L	Asthmatics, %	Duration of IP		Maximum Dose in IP	Efficacy of Desensitization	Maintenance Phase: Dose and Period of Follow-up	Maintained Tolerance: (N) Avoidance Diet Time and Efficacy (Passed OFC)[a]
					Programmed Mean	Final Mean (Range)				
Ojeda et al, 2012 [31]	Ac: 31 Con: 3 9.6 (6-15)	Not randomized, controlled Home-based protocol	Ac: OVA-sIgE: 8.4, OVM-sIgE: 9.92	NR	37 d	43 d	50 mL of liquid pasteurized WE	Ac: Total: 25/31 (80%) Partial: 1/31 (3.2%) Con: NR	1/2 raw egg, 3 times/wk NR	NR
Ruiz-García et al, 2012 [35]	Ac: 19 16 children: 7.9 (SD, 2.3) 3 adults: 28.3 (SD, 14.26)	Not randomized, not controlled	Egg-sIgE: 3.6, OVM-sIgE: 2.4	NR	63 d	49 d	2.8 g EW proteins	Total: 14/19 (73.7%)	≥3 WE/wk	NR
Meglio et al, 2013 [29]	Ac: 10 Con: 10 8.4 (4-14)	Randomized controlled Home-based protocol	Ac: OVA-sIgE: 11.3 (5.6-150), OVM-sIgE: 6.8 (1-150)	3 (33%)	181 d	212 d	Maximum: 25 mL raw egg	Ac: Total 8/10 (80%) Partial: 1/10 (10%) Failure: 1/10 (10%) Con: 20% (2/10)	Raw egg 3 times/wk or foods containing around 3 raw eggs/wk 6 mo	NR
Dello Iacono et al, 2013 [28]	Ac: 10 Con: 10 7.7 (5-11)	Randomized controlled Home-based protocol	Ac: EW-sIgE: 23.3 Con: EW-sIgE: 19.1	4 (40%)	176 d	NR	40 mL raw egg	Ac: Total: 0/10 (0%) Partial: 9/10 (90%) Failure: 1/10 (10%) Con: 0%	10-40 mL raw egg/d 6 mo	NR
Fuentes-Aparicio et al, 2013 [34]	Ac: 40 Con: 32 8.7 (5-15)	Randomized Controlled	Ac: EW-sIgE: 9.0, OVM-sIgE 7.98 (0.35-100)	28 (70%)	93 d	70 d (28-196)	10 g of DWE	Ac: 37/40 (92.5%) Tolerated 1 raw EW in OFC Ac: 6 mo after IP: 20/40 (50%) Con: 1 y from baseline: 7/32 (21.8%)	2 cooked eggs/wk 12 mo	NR
Vázquez-Ortiz et al, 2014 [24]	Ac: 50 Con: 32 8.3 (IQR, 3.9)	Not randomized, controlled	Ac: EW-sIgE: 6.44 OVM-sIgE: 5.68 (IQR, 20.8)	30 (64%)	112 d	Median: 135 d (IQR, 69)	One raw egg (60 g) 12 mo: tolerated 60 g	Ac: Total 40/50 (80) Partial 1/50 (2%) Ac: Total: 28/50 (56%) Partial: 4/50 (8%) Con: 5/32 (15.6%)	Up to 2 raw eggs/wk 12 mo of raw egg in DBPCFC	NR
Caminiti et al, 2015 [15]	Ac: 17 Con: 14 (placebo) 6 (4-10)	Randomized placebo controlled	Ac: WE-sIgE: 36.6 (5.2-110)	NR	112 d	112 d	4 g of DEW	Ac: 16/17 (94%)	2-3 eggs/wk 6 mo	(16) 3 mo Ac: 5/17 (29%) Con: 1/14 (7%)
Escudero et al, 2015 [21]	Ac: 30 Con: 31 8.7 (5-17)	Randomized controlled	Ac: EW-sIgE: 6.4 (1-245) OVM-sIgE 3.1 (0.7-162)	12 (41%)	63 d	Median: 32.5d (IQR, 14) 3/30 (10%) (102, 127 and 134 d)	2.8 g EW protein	Ac: 28/30 (93%)	1 undercooked egg/48-72 h 3 mo	(25) 1 mo Ac: 11/30 (37%) Con: 1/31 (3%)

Abbreviations: Ac, active group; Con, control group; d, days; DBPCFC, double-blind placebo-controlled food challenge; DEW, dehydrated egg white; DWE, dehydrated whole egg; EW, egg white; IP, induction phase; MP, maintenance phase; N number of patients undergoing avoidance diet and OFC; NR, not reported; OFC, oral food challenge; OVA, ovalbumin; OVM, ovomucoid; SBPCFC, simple-blind placebo-controlled food challenge; sIgE, specific serum IgE; WE, whole egg.

[a]Efficacy regarding patients in the active group as originally reported by authors. In some cases, these data are based on a per protocol analysis; in others, on an intention-to-treat analysis.. Outcome is assessed by intention-to-treat analysis.

factors, this extremely high variability in efficacy may depend on determinant factors such as patient profile (sIgE levels, age, asthma, threshold at baseline OFC) and protocol used (egg product, up-dosing, duration). Therefore, with the current methodology, variables cannot be stratified or analyzed separately without the risk of introducing bias.

Maintenance Dosing Phase: Maintained Tolerance Protocols and Efficacy

The maintenance phase consists of the regular administration of the same egg dose over a defined time period. The maintenance dose is usually the target dose for the induction phase. The administration interval also varies from once daily to every 2-3 days depending on the previously established target. This phase can last several months or years or may even be for the patient's lifetime.

Two well-defined strategies have been proposed for the maintenance phase. The first establishes a maintenance dose lower than the equivalent to 1 egg serving with the purpose of protecting the patient from inadvertent contacts with the food and to raise the food tolerance threshold above that established at the beginning of the egg OIT. This objective is confirmed over time using an OFC with doses higher than the dose given in the maintenance phase. The second strategy establishes a maintenance dose equivalent to a food serving (eg, 1 egg white or 1 whole egg). In addition to protecting the patient from inadvertent contacts, it enables egg to be added to the diet ad libitum, although in such a way that it must be maintained according to the physician's recommendations. For this reason, in some studies the allergen source used in the induction phase is substituted for the cooked natural food.

Most protocols establish a maintenance dose equivalent to 1 egg, which must be consumed by the patient every 1-3 days [21,24,29,30,32-34,36]. The patient can be advised to continue the consumption of raw egg [24,28,29,31], undercooked egg [21], cooked egg [33,34], or hard-boiled egg [38]. Some of the aforementioned studies allowed the patient to consume other foods containing egg [21,29,31-35]; other protocols established doses of less than 1 egg as maintenance treatment [16,17,19,20,28,31]. Studies using dehydrated egg white used doses varying from 300 mg (5% of an L-sized egg) [20] to 4000 mg of product [15]. Vickery et al [19] established a maintenance dose that could vary every 4 months according to the evolution of egg white sIgE levels (see above). Staden et al [17] used maintenance doses ranging between 1600 mg and 2800 mg of lyophilized egg protein, whereas the maintenance dose used by Ojeda et al [31] was 25 mL of liquid pasteurized whole egg (equivalent to half an egg) every 3 days. Protocols based on hard-boiled egg in the maintenance phase, prescribe regular intake of egg in cookies, flans, and creams [38].

Patients maintain desensitization only if they consume egg regularly during the maintenance phase. The duration of the maintenance phase varies considerably between studies, and in some cases it is not defined. Therefore, in such cases, it is unknown whether the desensitization status of patients is maintained over time [24,29,30,31,33,35] or only at the end of the induction phase [15-17,19-21,28,38]. In 2 protocols, the efficacy of desensitization was measured at the end of the induction phase and during the maintenance phase [34,36]. In both, efficacy was lower during the maintenance phase than at the end of the induction phase owing to adverse events leading some patients to leave the study. Itoh et al [36] stated that 50% (3/6) of patients eating 60 g of heated egg twice a week for more than 9 months did not tolerate 1 g of dehydrated egg white after the maintenance phase. Fuentes-Aparicio et al [34] reported that only 54% (20/37) of patients desensitized to 10 g of dehydrated whole egg (1 egg) at the end of the induction phase passed the OFC with raw egg white 6 months later. However, 92.5% (37/40) had tolerated this dose immediately after the end of the induction phase. This decrease in efficacy during the maintenance phase can be attributed to the use of cooked rather than raw egg, which was regularly administered during the induction phase, resulting in a loss of desensitization.

The ultimate goal of egg OIT is maintained tolerance. Few studies have analyzed whether the patient achieves maintained tolerance by following an egg exclusion diet. Most studies used food avoidance periods ranging from 1 to 2 months [16,17,19,21], and in 2 of the studies, the period of egg exclusion lasted for 3-4 months [15,20]. However, it is not known whether even these extended periods are long enough to guarantee lifelong food tolerance [18]. Staden et al [17] explored this concept for the first time after their patients received egg OIT or milk OIT for a mean of 21 months (induction phase plus maintenance phase). The patients then followed a 2-month egg-free or milk-free diet before undergoing a DBPCFC. Thirty-six percent of patients passed the DBPCFC. However, a similar percentage of patients (35%) in the control group passed the DBPCFC after a diet free of egg/milk for the whole study period, that is, they overcame their allergy spontaneously. Buchanan et al [20] reported 4 patients who passed a DBPCFC with 8 g of egg protein after 24 months receiving a low egg dose and who followed an egg-free diet for 3-4 months. Two of the 4 patients passed the second DBPCFC after the elimination diet. Following a similar methodology, Vickery et al [19] reported that 6 patients who passed a first DBPCFC after a mean maintenance phase of 33.8 months underwent a second DBPCFC after 1 month on an egg elimination diet. The dose administered during the DBPCFC was higher (10 000 mg) than the mean dose used in the maintenance phase (2050 mg). All patients passed this DBPCFC. Burks et al [16] showed that of the 30 children who tolerated 10 g of egg white in a DBPCFC at 22 months of the maintenance phase, 11 (28% of the total OIT group [40 patients]) passed an egg DBPCFC at 24 months followed by 4-6 weeks on an egg exclusion diet. At 30 and 36 months from the beginning of OIT, all children who had passed the last DBPCFC continued consuming egg without ARs. At 22 months from the beginning of OIT, the size of the skin test wheal for egg was inversely proportional and the egg-IgG4 levels were directly proportional to the probability of achieving a state of maintained tolerance. However, no correlation was observed between egg-sIgE levels or basophil activation at 22 months of treatment and the result of the DBPCFC. Caminiti et al [15] showed that 31% [5/16] of desensitized patients passed the DBPCFC after 10 months of egg OIT

(both phases) followed by 3 months on an egg exclusion diet, compared with 7% (1/14) of patients in the placebo group. Escudero et al [21] showed through DBPCFC that 37% (11/30) of patients initiating egg OIT (OIT for 3 months followed by an exclusion diet for 1 month) achieved maintained tolerance, compared with 3% (1/31) of patients in the control group. Egg white sIgE levels >7.1 kU_A/L prior to the beginning of the diet resulted in a 90% possibility that the patient would not pass the DBPCFC. Several studies have shown that patients receiving OIT who passed the OFC after an egg exclusion diet had lower egg sIgE levels than patients who did not [15,17,20,21].

In summary, studies report that 28% to 75% of patients receiving egg OIT may finally achieve maintained tolerance. Aspects such as duration of the maintenance phase, optimal egg dose, length of the egg avoidance period, and identification of predictors of maintained tolerance have not yet been determined.

Adverse Reactions

Safety is the most relevant factor to be taken into account if egg OIT is to be used in regular clinical practice. ARs are the cause of most of the failures and extensions of egg OIT protocols, because doses need to be repeated or decreased, thus leading to delays. Analysis of safety is complex, since there is no consensus on how to classify and report ARs in OIT. The most frequent classifications used are those proposed by Sampson et al [39] and Clark and Ewans [40], which are based on the severity of the reaction. Authors sometimes report the percentage of patients experiencing ARs, although they also report the percentage of ARs compared with the total dose administered throughout the treatment. Table 3 shows a summary of the adverse reactions in egg oral immunotherapy protocols.

In all studies but one [15], the percentage of patients with at least 1 AR during treatment is high (50%-100%). The percentage of doses producing ARs also differs widely between studies. Escudero et al [21] report ARs to 5.9% of doses, while Burks et al [16] report a 25% incidence.

In most cases, over 80% of the reactions during OIT are mild to moderate; serious reactions are rare or nonexistent [16,19,21,31,33,34,36]. Some articles record the number of epinephrine doses administered to treat adverse reactions during OIT.

However, deducing the severity of ARs based on the number of epinephrine doses may lead to errors. In some cases, there is no concordance between the number of severe ARs and the number of epinephrine doses administered. Of note, epinephrine is administered based on the investigator's criteria, which may differ from international guidelines [41].

The most frequent ARs described in egg OIT are gastrointestinal (>20% of ARs in all studies) [20,21,24,31,34,36], although in some studies [16,17,28,29,33] oropharyngeal and cutaneous symptoms are more prominent (Table 3).

Few studies report ARs during the maintenance phase [16,21,24]. Vazquez-Ortiz et al [24] reported the same frequency of ARs for both phases, although they acknowledge that 13 epinephrine doses were necessary during the induction phase, compared with none during the maintenance phase. Both Escudero et al [21] and Burks et al [16] agree that moderate reactions are far less frequent during the maintenance phase and that no severe ARs were observed in the maintenance phase (Table 3).

Some non–IgE-mediated reactions have not been considered ARs. Since the first report of OIT-induced eosinophilic esophagitis [42], more cases have been reported, including ARs to egg OIT [34,43]. The incidence of eosinophilic esophagitis due to OIT is estimated at 2.7% [44]. As for atopic dermatitis, only 1 report [16] discusses the case of a patient whose treatment failed owing to the exacerbation of pre-existing eczema. The authors also describe anxiety as an AR during egg OIT.

Many cofactors may be involved in ARs to a previously well-tolerated dose after the consumption of egg during OIT. The most frequently identified cofactors are physical exercise [15,17] and infections [15,17,29]. Other cofactors include poor adherence to OIT [17,30,33], stress [33], menstruation [33], and hay fever [17].

Several attempts have been made to find clinical and/or biological markers to identify patients who are more prone to ARs during egg OIT. The risk factors identified to date as being related to anaphylaxis or early discontinuation of egg OIT are severity of symptoms (respiratory symptoms, anaphylaxis, and/or Sampson grade 4 severity) during baseline OFC, previous diagnosis of asthma [24], and high baseline egg sIgE levels [17,21,24]. Published cutoffs for sIgE that predict a higher risk of ARs are egg white sIgE and ovomucoid sIgE >8.85 kU_A/L and ovalbumin sIgE >6.49 kU_A/L [24].

Premedication with second-generation oral antihistamines has been administered to avoid oropharyngeal symptoms and mild reactions and may also improve adherence to OIT [31]. Furthermore, inhaled corticosteroids minimize bronchospasm in asthmatic patients and events caused by respiratory infections, thus weakening their impact as cofactors [24,31]. Abdominal pain can be treated with sodium cromoglicate, although its efficacy is controversial [16].

Most ARs in egg OIT are mild and moderate, and serious reactions are only rarely present; however, the number of adverse events and patients experiencing them is quite considerable. In addition, the way ARs are reported does not enable us to draw robust conclusions. A consensus on how to treat and report such events should be addressed.

Immunological Changes

The immunological mechanisms involved in the clinical changes observed during egg OIT are not entirely clear. A decrease in the dimensions of the wheal produced by skin prick testing with egg white after 4 months of the maintenance phase has been reported [19], although not all authors observed this change [36]. After 6 months in the maintenance phase, there is a clear, statistically significant difference in skin prick test results for both egg white [29] and whole egg compared to baseline [28,33]. This decrease in size is maintained at 10 months [15] and at 22 months and has also been reported after maintained tolerance has been achieved [16].

Several authors found no differences in desensitized children when comparing baseline egg white sIgE, ovalbumin

Table 3. Adverse Reactions in Egg Oral Immunotherapy Protocols

	No. of Patients	Adverse Reactions			Severity						Symptoms Perceived, % of ARs					
		No. of ARs	No. (%) of Patients	Doses With ARs, %	Mild		Moderate		Severe		GI	OPS	Skin	Rhinitis	Resp	Anaph
					ARs, %	Patients, %	ARs, %	Patients, %	ARs, %	Patients, %						
Staden et al [17]	25	47	25 (100)	[a]		84		16		0	25.5	6.38	59.57	4.25	4.25	0
Buchanan et al [20]	7	7	7 (100)			57.1		28.6		14.3	71.4	14.3	28.6	14.3	0	14.3
Vickery et al [19]	6	12	5 (83)		66.6[b]		33.3[b]		0		33.3	25	25	8.33	8.33	0
Itoh et al [36]	6	7	6 (100)		71.4		28.6		0		42.8	0	14.28	0	42.8	0
Fuentes-Aparicio et al [34]	40	36	21 (52.5)		22.2		61		0		50	16.66	5.55	2.77	11.11	13.88
García-Rodríguez et al [33]	23	55	18 (78.3)		63.63		36.36		0		24.07[b]	17.59[b]	31.48[b]	23.14[b]	3.70[b]	0
Ojeda et al [31]	31	180	22 (74.19)		86.1		13.9		0		55.1	15.8	13.8	6.6	3.6	3.6
Meglio et al [29]	10	79	7 (70)								21.51	46.8	10.12	21.51	0	
Dello Iacono et al [28]	10	53	10 (100)	14	24.5		66		9		33.9	39.62	43.39	32.07	9.43	0
Vázquez-Ortiz et al [24] Total	50	1024	45 (90)	7.6	61.2		38.8		0.09		37.2	13.7	20.5	7.7	18.8	2.1
IP		503														
MP		521														
Caminiti et al [15]	17	3	3 (17.64)		66.6		0		33.3		33.3		33.3			33.3
Escudero et al [21]	30	145	21 (70)	5.9	98		2		0		66.9	33.6	4.9	22.1	3.4	0

	No. of Patients	Doses Causing ARs, %	Severity of ARs According to Dose, %			Symptoms Perceived According to Doses Administered, %					
			Mild	Moderate	Severe	GI	OPS	Skin	Rhinitis	Resp	Anaph
[c]Burks et al [16]	40	25	14.3	0.7	0	5.5	15.4	4.4	0	7.8	0
IDDE		27.4	16.7	3.7	0	5.5	13.8	8.1	0	9.8	0
Build-up		35.9	22.1	1.9	0	8.8	19.7	5.8	0	13.4	0
MP		24.2	13.7	0.6	0	5.1	15.1	4.2	0	7.4	0
[c]Escudero et al [21]	30	5.9	98	2	0	4	2.2	0.3	1.3	0.2	0
IDDE		5.9	100	0	0	3.4	3.4	0	3.4	0	0
Build-up		6.1	96	4	0	5	1.3	0.2	0.7	0.4	0
MP		5.7	100	0	0	2.5	3	0.5	1.4	0	0

Abbreviations: Anaph, anaphylaxis; AR, adverse reaction; GI, gastrointestinal; IDDE, initial day dose escalation; IP, induction phase; MP, maintenance phase; No, number; OPS, oropharyngeal symptoms; Resp, respiratory symptoms.

[a]Blank cells correspond to data not reported.

[b]Data not expressed directly by the authors, but obtained subsequently from published data.

[c]Adverse reactions are expressed according to the percentage of administered doses reported.

sIgE, and ovomucoid sIgE values with values observed during treatment [15,16], at the end of the induction phase, at 6 months, and at 12 months [34], as well as in cases where tolerance is maintained [16]. However, other studies described an intragroup decrease in median ovalbumin sIgE and ovomucoid sIgE [19,29] at the end of the induction phase, and in egg white sIgE [36] at 6 months [19,28,33], 12 months [36], and 24 months [20]. It is generally accepted that levels of egg sIgG4, ovalbumin sIgG4 [29], and egg white sIgG4 [19] increase over time and at very early stages, even from the third week after the end of the induction phase [15,33,34], remaining over baseline values at 12 months [36], 22 months, and when maintained tolerance is reached [16]. However, no differences were described in ovomucoid sIgG4 values during treatment [29]. Only 1 study has assessed possible changes in ovalbumin sIgA and ovomucoid sIgA, although the authors failed to find any significant associations [45].

Decreased expression of CD63 correlating with decreased basophil activation in desensitized children has been observed [46]. Burks et al [16] also reported a decrease in basophil activation after 22 months of treatment, although no statistically significant relationship with maintained tolerance was observed.

As for changes in cytokine secretion, a significant increase in IL-5 was detected immediately after the induction phase [29]. No differences were detected in the secretion of IL-4, IL-6, IL-12, IL-13, IFN-γ, TNF-α, TGF-β1, or TGF-β2 [19,29,36,47]. Results for secretion of IL-10 are contradictory, since some studies reported a decrease [36], whereas others reported an increase [19] or no change [29]. A statistically significant decrease in expression of IL-9 has been reported after egg OIT [47].

Despite the diversity of immunological changes reported to result from egg OIT, there is some unanimity regarding the decrease in the size of the skin test wheal and the levels of egg white sIgE and a significant early increase in egg white sIgG4. Some of these differences (especially early changes) seem more likely to be due to the different durations of the induction phase, which ranged from 5 days to more than 300 days. Moreover, the maintenance dose and the extract used might affect the trend of such biomarkers. Further studies are necessary to elucidate the immunological mechanisms involved in egg OIT, both for desensitization and for maintained tolerance.

Conclusions

Egg-allergic patients are at daily risk of accidental exposures that can result in life-threatening reactions. Egg OIT is a promising and potentially disease-modifying approach for egg allergy. Most studies demonstrate the ability of OIT to induce desensitization to egg, with success rates ranging from 0% to 100% (median success rate of >80%). Maintained tolerance, a goal beyond desensitization, is explored by few authors and has been achieved in 28% to 75% of treated patients. In addition, maintained tolerance entails normalization of the diet. Egg OIT is not free of risks, and most patients experience ARs, although these are not usually severe. Immunological changes resulting from egg OIT have been reported and include a decrease in the size of the skin test wheal and egg white sIgE levels and a significant early increase in egg white sIgG4. Methodological differences in published studies prevent us from drawing robust conclusions for key variables (eg, indications, protocols, and safety) and from implementing this approach in regular practice. Both these and other poorly studied variables (eg, immunological mechanisms involved, impact on quality of life, and cost-effectiveness of treatment) should be further investigated.

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Conflicts of Interest

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