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Egg oral immunotherapy in children (SEICAP I): Daily or weekly desensitization pattern

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Abstract

Background: Studies are required before incorporating egg oral immunotherapy (OIT) into clinical practice. The Spanish Society of Pediatric Allergy, Asthma and Clinical Immunology (SEICAP) conducted a multicenter, randomized controlled study assessing the effectiveness and safety of the OIT using pasteurized egg white (PEW) in egg-allergic children.

Methods: One hundred and one egg-allergic children (6-9 years) were randomized for 1 year: 25 to an egg-free-diet (CG) and 76 to OIT (target dose 3.3 g PEW proteins), PI (30% weekly plus 5% daily increments) or PII (only 30% weekly increments) buildup patterns. Egg skin prick test, sIgE and sIgG4 serum levels, PEW double-blind placebo-controlled food challenge (DBPCFC), and dosing adverse reactions (DARs) were evaluated in all patients from inclusion (T0) until completing 1 year of follow-up (T12). At T12, egg-allergic control patients could start OIT. The effectiveness and safety of OIT and the effect of the buildup pattern were analyzed.

Results: At T12, 4/25 (16.0%) CG patients passed the PEW DBPCFC vs 64/76 (84.2%) OIT that reached total desensitization ($P = 0.000$); 12 egg-allergic control patients started OIT. Finally, 72/88 (81.81%) patients reached total desensitization, 96.15% PI vs 75.80% on PII ($P = 0.01$). Induction period (121.12 ± 91.43, median 98.00 days) was longer in patients on PII buildup pattern, and those with allergic asthma, minor threshold dose, or higher egg sIgE ($P < 0.05$). Most patients (89.06%) developed DARs: 74.53% were mild; 21.90% moderate; and 3.5% requiring adrenaline-treatment. Moderate reactions and those requiring adrenaline were more frequent in patients with allergic asthma, PII pattern, or higher egg sIgE serum antibody levels ($P < 0.05$).

Conclusions: PEW OIT is an effective treatment for children with persistent egg allergy. A 30% weekly plus 5% daily increment pattern could be more effective and safer than one with only 30% weekly increments.

KEYWORDS

buildup phase OIT patterns, desensitization, effective egg OIT, egg allergy, egg oral immunotherapy, safe egg OIT

1 | INTRODUCTION

Egg allergy is one of the most common food allergies in Western countries, affecting up to 2% of young children.[1] Over 50% of children with egg allergy develop natural tolerance at the age of 5, but for some, egg allergy can persist beyond adolescence.[1-3]

Oral immunotherapy (OIT) has been shown to be an effective treatment to induce desensitization in patients with egg allergy.[4-7] However, OIT is a long-term treatment with associated dose adverse reactions (DARs), which are typically related to the buildup desensitization phase,[8] requiring close medical monitoring. Rush OIT protocols are shorter, but they have been associated with more frequent and severe DARs than slower protocols.[9-11] However, slower protocols could reduce treatment adherence. The heterogeneity of the studies (age of the studied population, differences in diagnosis, materials, the length, and results of immunotherapy protocols) makes it difficult to choose the best protocol for clinical practice.

The Spanish Society of Pediatric Allergy, Asthma and Clinical Immunology (SEICAP) conducted a multicenter, randomized controlled study of OIT in children with proven persistent egg allergy, investigating the best OIT strategy, the most effective and safe protocol to reach total desensitization and how to maintain this state once the diet has been normalized. This study has been divided into two parts: SEICAP I, assessing induction of desensitization; and SEICAP II, which studies two maintenance OIT patterns and the effect of a normalized diet on the desensitization state once the OIT has ended.

The purpose of the first part of the study (SEICAP I) was to assess the effectiveness and safety of OIT, with a homogeneous study: in egg-allergic children (6-9 years), using PEW for OIT (target dose equivalent to one medium-sized egg or 3.3 g protein), and to prove the allergy or desensitization state throughout the study by PEW DBPCFC. We took advantage of this study to assess two similar buildup desensitization patterns, seeking improvements in the induction phase.

2 | METHODS

2.1 | Study design and participant selection

The primary aim of this randomized study (SEICAP I) was to examine the effectiveness and safety of egg OIT with PEW in children with egg allergy (6-9 years) reaching total desensitization (3.3 g PEW protein) vs a control group (CG) reaching natural tolerance on an egg-free diet for 1 year. Total desensitization was defined as the ability to pass an oral food challenge with PEW equivalent to one medium-sized egg (3.3 g protein) while still receiving daily oral immunotherapy. Safety was evaluated according to the rate of total dosing adverse reactions (DARs) and their grades, which were assessed according to Sampson's grading.[12] We also compared the effectiveness and safety of two similar OIT induction patterns: PI (30% weekly and 5% daily up-dosing) vs PII (30% weekly up-dosing, but no extra daily up-dosing). This subgroup of analysis included patients randomized at inclusion (T0) to OIT and those patients randomized to the CG at T0 who did not pass the PEW DBPCFC after 1 year (T12) and then started OIT.

The secondary objective was to assess the impact of the following clinical and immunologic factors on the effectiveness and safety of the OIT: atopic diseases, previous cooked egg tolerance, threshold dose response, egg white (EW) skin prick test (SPT), and egg sIgE and sIgG4 at baseline.

2.1.1 | Sample size, patient selection, and randomization

We calculed that a sample of 101 egg allergic children, 76 patients reciving egg OIT (38 A and 38 B maintenance) and 25 control group (CG) on an egg free diet over one year, could detect significant differences.

Patients with a diagnosis of egg allergy were recruited from the allergy units of the Spanish children's hospitals of the public health care system, and their parents were informed and invited to participate in this study previous assessment of inclusion and exclusion criteria.

Inclusion criteria: (1) children aged 6-9 years with a previous diagnosis of egg allergy and at least one allergic reaction to egg over the last year; (2) parents having signed informed consent to participate in the study; (3) positive EW SPT (EW 10 mg/mL) mean weal diameter >3 mm; (4) specific sIgE serum levels above 0.35 KU/L to EW, ovalbumin (OVA), or ovomucoid (OVM); and (5) egg allergy confirmed by a PEW DBPCFC at the time of inclusion.

Exclusion criteria: (1) severe or uncontrolled asthma[13]; (2) severe atopic dermatitis according to the objective severity scoring of atopic dermatitis index[14]; (3) esophagitis symptoms; (4) autoimmune, cardiovascular, or neuropsychiatric diseases; (5) beta-blocker treatment; (6) food OIT during the last year; and (7) immunotherapy with airborne allergens in the start-up phase.

2.1.2 | Study protocol

The study protocol and consent forms were approved by the institutional review board of the Spanish Public Health Care System (EC3250) of La Paz University Hospital (Madrid) and then by all the other participating hospitals. Written informed consent was obtained from the parents or guardians, with assent from children older than 7 years.

Patients meeting all the inclusion and none of the exclusion criteria were included and randomized at T0, by means of a centralized computer algorithm, to OIT (A or B maintenance groups) or to an egg free diet (control group or CG) for one year. (Table S1 in the repository).

The study was developed over 1 year. Treatment for asthma control was continued during the study, and no other medication was given. Clinical and immunologic markers were evaluated and egg challenges were performed throughout the study (Table S2 in the repository).

2.1.3 | Immune markers

Skin prick tests (SPTs) were performed with EW extract (10 mg/mL), with saline and histamine as negative and positive controls, respectively (Diater Laboratories S.A., Spain). The weal size was calculated using the average of the largest and the perpendicular midpoint diameter (D[mm]+d[mm])/2) and then subtracting the size of the saline weal. Total IgE, specific (EW, OVA, and OVM) IgE, and EW sIgG4 serum antibody levels were measured with the use of ImmunoCAP 100 (Thermo Fisher Scientific).

2.2 | Oral food challenge

Egg allergy and the desensitization state were confirmed by an egg DBPCFC blinded with potato, carrot, and olive oil mashed together. Challenges were performed in a hospital setting and supervised by a physician. At T0, a DBPCFC with one boiled EW (at 100°C for 10 minutes) was performed for all patients, starting with a dose of 2.5 g, and then increasing the dose every 30 minutes: 5, 10, and 25 g (0.183, 0.366, 0.733, and 1.833 g protein), up to an accumulated dose of 45 g (3.30 g protein). On the following day, a second PEW DBPCFC was performed, starting with 1 mL, and then increasing the dose every 30 minutes: 2, 4, 8, and 15 mL (0.11, 0.22, 0.44, 0.88, and 1.65 g protein), up to an accumulated dose of 30 mL (3.3 g protein) corresponding to one medium-sized egg. If allergic symptoms did not appear 2 hours after the intake of the final dose, the patient was discharged. The challenge was stopped if the patient developed urticaria/edema, severe abdominal pain, vomiting, rhinitis, bronchospasm, or hypotension; the reaction was treated and the patient was discharged 6 hours after controlling the reaction.

An open challenge with one raw egg was performed for OIT patients 24 hours after they reached total desensitization and at T12 for all control and OIT patients, 48 hours after passing the PEW DBPCFC. This raw egg challenge was conducted at breakfast using cow's milk in a milkshake (soy or oat milk can be used if the patient was allergic to either cow's milk or soy).

2.3 | Oral immunotherapy protocol

PEW (Guillen, Valencia, Spain), whose allergenicity has been proven equivalent to raw EW,[15] was used for the OIT (Table 1). Desensitization protocol was performed in 3 phases: (1) the initial dose escalation phase that was performed in hospital, starting with 1 mL of a 1/1000 water solution of PEW (0.11 mg protein); if the patient did not develop allergic symptoms, a double dose was

TABLE 1 Immunotherapy protocol: (1) The initial dose escalation phase was performed in the hospital; (2) the buildup phase was performed with 30% weekly up-dosing over the last tolerated dose in hospital, pattern I (PI) with an additional 5% daily up-dosing over the last tolerated dose at home for a week and pattern II (PII) with the last tolerated dose in hospital daily at home for a week, until reaching the target dose (30 mL of PEW, 3.3 g protein) equivalent to one medium-sized egg; and (3) the maintenance phase was as follows: daily 30 mL PEW at home for patients randomized to A maintenance and every 2 d for patients randomized to B maintenance

Initial dose escalation phase in hospital*		
Water solution	mL	Protein (mg)
1/1000	1	0.11
	2	0.22
	6	0.66
1/100	2	2.2
	4	4.4
1/10	1	11
	2	22
1/1	0.4	44
Buildup phase up to reach 30 ml (3.3 g protein)		
Pattern I • In hospital: 30% weekly up-dosing over the last tolerated dose. • At home: 5% daily up-dosing over the last tolerated dose		Pattern II • In hospital: 30% weekly up-dosing over the last tolerated dose. • Daily dose at home is the last tolerated dose in hospital (no extra daily up-dosing)
Maintenance phase completing one OIT year 30 mL PEW dose per day (patients randomized to the A maintenance group) 30 mL PEW dose every two days (patients randomized to the B maintenance group)		

*A water solution of PEW was administered every 30 min up to 0.4 mL (44 mg protein) or until symptoms appeared. If the patient had a mild reaction, the previously tolerated dose was given before resuming the process. If significant symptoms developed, the rush phase was stopped, and the patient was treated for reactions as needed, observed for 2 h, and then discharged. The rush phase was continued in the hospital the following day, beginning with 2 previous step doses.

OIT, oral immunotherapy; PEW, pasteurized egg white; up-dosing, incremented doses.

administered every 30 minutes until reaching undiluted PEW, and the patient was discharged 2 hours later if he did not develop DARs. The next day, the patient received the last tolerated dose in the hospital; if this was tolerated again, it was the daily dose took at home for a week. (2) The buildup phase was started with a pattern based on 30% weekly increments in hospital over the last tolerated dose. This was the daily dose taken at home for a week in patients following PII buildup pattern. Since one of the participating centers (La Paz Hospital) had positive results with a protocol of 30% weekly increments in hospital plus 5% daily increments at home over the last tolerated dose, the design of the study allowed this variation in the OIT protocol (PI buildup pattern) only for those patients included

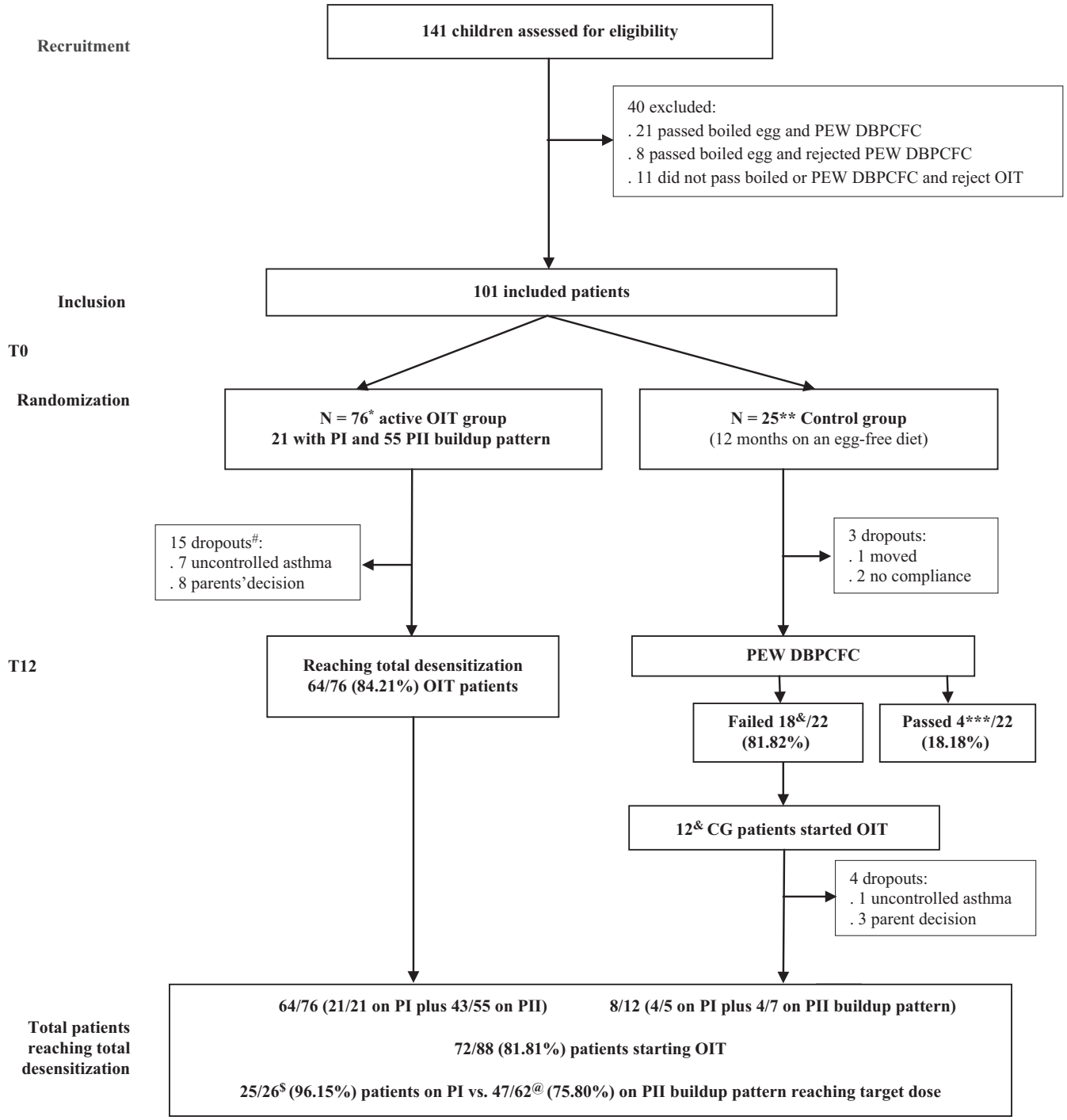

FIGURE 1 Flowchart. Evolution of patients through the study. OIT: oral immunotherapy; PEW: pasteurized egg white; DBPCFC: double-blind placebo-controlled food challenge; *14 OIT patients passed boiled egg DBPCFC at T0; **2 control patients passed boiled egg DBPCFC at T0; #2 had passed boiled egg DBPCFC at T0; ***2 had passed boiled egg DBPCFC at T0; &1 had passed boiled egg DBPCFC at T12; $5 had passed boiled egg DBPCFC at the beginning of the OIT; @9 had passed boiled egg DBPCFC at the beginning of the OIT

by this center. These increments (PI or PII patterns) were repeated until reaching total desensitization, which will be considered to have occurred when the target dose 30 mL PEW (3.3 g protein) will be reached without allergic symptoms for at least 2 hours. The next day, an open food challenge in the hospital with a raw egg confirmed total desensitization. (3) The maintenance phase was as follows: All patients who reached total desensitization completed the OIT year with 30 mL PEW daily or every 2 days, according to the maintenance assigned at inclusion (A or B) (the effect of maintenance treatment after stopping OIT will be reported on the SEICAP II manuscript).

If DARs occurred, the protocol was readapted: For grade 1 DARs, the pattern was continued; for grade 2, the same dose was repeated on the following day; and if the reaction was greater than grade 2, a reduced (1-3 steps) dose was administered in the hospital on the following day. When inflammatory or infectious processes appeared, OIT was stopped. If OIT had been stopped for less than 48 hours, it was restarted with the last tolerated dose; if it stopped for more than 48 hours and less than 4 days, it was restarted in the hospital with 50% of the last tolerated dose; and if it stopped for 5 or more days, OIT was reestablished in the hospital with less than 30% of the last tolerated dose (Table S3 in the repository).

The patients and their families were instructed to avoid potential risk factors for adverse reactions: Children treated with OIT were under observation for at least 4 hours after receiving each dose; OIT was the only egg consumption allowed until reaching total desensitization; and physical exercise was restricted from one hour before and up to 4 hours after receiving the corresponding dose of PEW and nonsteroidal antiinflammatory drugs from 4 hours before and up to 4 hours after receiving the dose. The parents were trained in recognition and treatment of reactions according to the European Academy of Allergy and Clinical Immunology Anaphylaxis Guidelines.[16] Epinephrine autoinjectors and instructions on their use were provided to the parents, and they were asked to complete daily home diaries, which were reported weekly or at follow-up visits to the investigators.

2.3.1 | Follow-up

During the buildup phase, all OIT patients had weekly visits in hospital. Before receiving the corresponding dose with the weekly increase, the investigator reviewed the patient's diary, collected a detailed clinical history, and performed a physical examination and baseline spirometry to check the compliance and health status of the patients. In addition, OIT patients had follow-up visits 6 and 12 months after the inclusion/beginning of the OIT (at T6 and T12) and control patients only had visits at T0 and T12. These visits also included EW SPT, and evaluation of egg (EW, OVA, and OVM) sIgE and EW sIgG4 antibody serum levels. At T12, a PEW DBPCFC was performed to all control patients who had previously passed a boiled egg DBPCFC and to all OIT patients who had reached total desensitization. At this time all patients that passed the PEW DBPCFC, performed 48 hours later, an open raw egg challenge (Table S2 in the repository).

2.4 | Statistical analysis

A two-group continuity correction chi-square test calculated that a sample of 101 participants (76 receiving OIT—38 A maintenance and 38 B maintenance; and 25 on an egg-free diet for 1 year) would provide 80% power, at a one-sided alpha level of 0.05, to detect a significant between-group difference in the rate of unresponsiveness, assuming an estimated success rate of 20% in the CG and 50% in the OIT group. Clinical outcomes were assessed by intention-to-treat and per-protocol analyses. The chi-square test was used to compare patients reaching total desensitization in the OIT group or development of natural tolerance in the CG over 1 year. The Mann-Whitney test was used to test for differences between the OIT and CG and the PI and PII buildup group patients. The Wilcoxon rank-sum test was used to evaluate between-group differences in the SPT (weal size) and in immunoglobulin serum levels. General linear regression model (GLM) was used to evaluate the association of selected immune variables with clinical outcomes. All analyses were performed with the use of SAS software 9.3 (SAS Institute, Cary, NC, USA).

3 | RESULTS

Nine allergy units from the Spanish Public Health Care System participated in this study, including 101 participants who met all the inclusion and none of the exclusion criteria (median age 6 years and 9 months). Most participants, 94/101 (93.06%), reported other allergic diseases: 72 (71.28%) atopic dermatitis; 60 asthma (59.40%), 40 of them allergic asthma; and 70 (69.30%) other food allergies, with half of them to more than two foods. At inclusion, 16 children (15.84%) passed and 85 did not pass the boiled egg DBPCFC. Children with allergy to boiled egg showed higher OVM sIgE and lower EW sIgG4 serum antibody levels than those passing the boiled egg DBPCFC ($P < 0.05$); there were no differences in the PEW threshold dose response, EW SPT weal, or total or specific EW and OVA sIgE serum antibody levels (Table S4 in the repository).

3.1 | Effectiveness and safety of PEW OIT

3.1.1 | Patients at T0 randomized to OIT vs control group

At baseline, the patients randomized to OIT were older than control patients ($P = 0.013$), but there were no differences in the other atopic diseases or the tolerance to boiled egg rate, the threshold dose, the EW SPT weal, and the EW, OVA, or OVM sIgE or EW sIgG4 serum levels (Figure 1; Table 2).

3.1.2 | Effectiveness

At T12, 4/25 (16.00%) of the total control patients, or 4/22 (18.18%) controls that reached T12, passed the PEW DBPCFC vs

64/76 (84.21%) OIT patients who had reached the target dose or total desensitization. ($P = 0.000$). The mean induction period was 121.12 ± 91.43 days, median 98.00 (7-329) days, and the mean of total doses during buildup phase was 148.60 ± 60.87, median 96.00 (7-329). All control and OIT patients who passed the PEW DBPCFC at T12 passed 24-48 hours later the open raw egg challenge. Twelve of the CG patients with egg allergy at T12 requested and started egg OIT at this time (Figure 1 and Table 3).

Withdrawals and dropouts

Fifteen patients dropped out of the study: Three patients in the control group did not achieve T12 (one was moved, one rejected the PEW DBPCFC due to an egg-allergic reaction 2 months before reaching T12, and another was withdrawn due to noncompliance with the protocol) and twelve patients discontinued OIT because of DARs (seven were withdrawn by researchers because of their uncontrolled asthma, and five dropped out due to the parents' decision) two of them had passed the boiled egg DBPCFC at baseline (Figure 1). At T0, these patients had lower threshold response dose, higher allergic asthma rate, larger EW SPT weal, and higher egg sIgE serum antibody levels ($P < 0.05$). At the time of the OIT interruption, these patients had had higher rate of DARs requiring adrenaline treatment than patients who reached total desensitization ($P < 0.05$) (Table 3).

3.1.3 | Safety data

Most OIT patients developed DARs during the buildup phase 69/76 (90.78%), 57/64 (89.06%) children who reached the target dose; 420/8448 (4.97%) doses triggered obvious allergic reactions). Reactions were more frequently associated with dose increments and some when an infectious process or emotional stress was suspected or coinciding with exercise, and 17 patients had reactions without other known associated factors ($P < 0.05$). Most reactions 313/420 (74.53%) were grade 1 or 2, fifty seven patients had between 1-56 of these reactions; 92/420 (21.90%) were grade 3, twenty nine patients had (1-14) ; 15/420 (3.57%) were grade 4 reactions, seven patients had (1–3) of these reactions and all of them were controlled with one adrenaline dose, systemic corticosteroids and anti-H1 drugs (Table 4). No patients developed dysrhythmia and/or severe hypotension, hypovolemic shock, laryngeal edema, or respiratory or cardiac arrest.

Four CG and two OIT patients had moderate reactions (grade 2-3), which resulted from accidental egg exposure.

3.2 | Analysis PI vs PII OIT patterns

Finally, 88 children with egg allergy started egg OIT (26 on PI and 62 on PII buildup pattern). At T0, 76 had been randomized to OIT and 12 to controls, but these control patients did not pass the PEW challenge at

TABLE 2 Comparison of **c**linical characteristics and immune markers at inclusion (T0) of patients randomized to an egg-free diet (control group) vs OIT (OIT group)

	At inclusion (T0) N = 101 patients				
	Control group (CG) N = 25		OIT group N = 76		*P* value
Male/female rate	12/13		36/40		1.00
Asthma	14/25 (56.00%)		45/76 (59.21%)		0.860
Allergic asthma	7/25 (28.00%)		23/76 (30.7%)		0.937
Atopic dermatitis	18/25 (72.00%)		54/76 (71.1%)		0.709
Boiled egg tolerance at T0	2/25 (8.00%)		14/76 (18.42%)		0.511
	Mean ± SD	Median (min-max)	Mean ± SD	Median (min-max)	
Age (months)	75.24 ± 11.69	76 (70-96)	81,42 ± 12,50	84 (72-109)	0.013
Threshold dose (PEW g proteins)	0.31 ± 0.21	0.26 (0.02-0.66)	0.43 ± 0.52	0.22 (0.11-2.00)	0.287
EW SPT weal (mm)	8.65 ± 2.20	8.25 (4.00-12.00)	8.15 ± 2.51	8.00 (4.0-14.0)	0.421
Total IgE (KU/L)	569.60 ± 456.15	434.00 (31-1756)	777.16 ± 1242.72	491.50 (10-10801)	0.440
EW sIgE (KU/L)	21.46 ± 32.51	8.06 (0.02-101.00)	38.52 ± 208.27	6.44 (0.22-2045.00)	0.450
OVA sIgE (KU/L)	12.83 ± 21.28	4.01 (0.01-80.10)	26.39 ± 152.94	3.65 (0.10-1496.00)	0.618
OVM sIgE (KU/L)	19.02 ± 29.24	7.28 (0.01-121.02)	15.37 ± 24.81	5.18 (0.10-101.00)	0.201
EW sIgG4 (mg/L)	0.76 ± 1.03	0.16 (0.06-2.79)	1.82 ± 2.75	0.29 (0.04-20.10)	0.292

PEW, pasteurized egg white; DBPCFC, double-blind placebo-controlled food challenge; SPT, skin prick test; weal (mm), perpendicular midpoint diameter (D[mm]+d[mm])/2)mm, subtracting the size of the saline weal; EW, egg white; OVA, ovalbumin; OVM, ovomucoid; sIgE, specific IgE antibody levels; sIgG4, specific IgG4 antibody levels.

TABLE 3 OIT patients: patients reaching total desensitization vs dropouts/withdrawals. Baseline clinical characteristics and immunologic markers

	Withdrawals/dropouts N = 12		Total desensitization N = 64		*P* value
Age	79.87 ± 13.48		78.17 ± 11.360		0.677
Sex (male/female)	6/6		30/34		0.762
Other food allergies	5/12 (43.75%)		41/64 (63.88%)		0.262
Allergic asthma	4/12 (37.50%)		21/64 (33.33%)		0.013
	Mean ± SD	**Median (min-max)**	**Mean ± SD**	**Median (min-max)**	
Threshold dose (g PEW proteins)	0.159 ± 0.089	0.135 (0.080-0.330)	0.560 ± 0.609	0.370 (0.022-2.500)	0.003
EW SPT weal (mm)	8.23 ± 2.42	8.50 (4.00-14.0)	9.25 ± 2.46	9.75 (5.00-12.50)	0.177
EW sIgE	68.41 ± 62.73	48.50 (4.04-227.00)	33.34 ± 217.37	5.47 (.02-2145.00)	0.000
OVA sIgE	45.55 ± 40.11	28.25 (1.94-101.00)	22.98 ± 159.96	2.71 (.00-1496.00)	0.000
OVM sIgE	56.61 ± 38.37	48.90 (5.18-101.00)	9.46 ± 14.90	3.00 (.0189.00)	0.000
DARs requiring adrenaline treatment	N patients 3/12 (25.00%)	N reactions/patient 2-3	N patients 2/64 (4.16%)	N reactions/patient 1-2	0.013

Total desensitization, OIT patients reaching target dose (3.3 g PEW proteins); N, number; withdrawals/dropouts, patients who dropped out or were withdrawn from OIT; threshold dose (g PEW proteins), minimum dose that induced an immediate allergic reaction at the time of inclusion; EW, egg white; SPT, skin prick test; weal (mm), perpendicular midpoint diameter (D[mm]+d[mm])/2); OVA, ovalbumin; OVM, ovomucoid.

T12, and then required and started OIT. At T0, PI and PII patients had a similar rate of boiled egg tolerance, allergic asthma, and atopic dermatitis, and they did not show differences in threshold dose, EW SPT, or total IgE or EW sIgG4 serum levels. Patients on the PII pattern, however, had higher EW, OVA, and OVM sIgE serum levels ($P < 0.05$; Table 5).

3.2.1 | Effectiveness

Most patients, 72/88 (81.8%), reached total desensitization; the desensitization rate was similar in the patients who passed or who did not pass the boiled egg challenge before starting the OIT 12/14(85.71%) vs 60/74 (81.08%). Patients on PI had higher desensitization rate than the patients on PII buildup pattern, 96.15% vs 75.80% ($P = 0.01$) and a shorter induction period (median 65.00 (27-154) vs 126.00 (7-329) days ($P = 0.000$). A general linear regression model confirmed that the OIT patterns showed difference for the induction period, adjusted to EW, OVA, and OVM sIgE antibody serum levels ($P = 0.001$); (Figure 2). Nevertheless, PI patients received more total up-dosing, although they required less 30% weekly up-dosing than patients on the PII buildup pattern ($P < 0.05$) (Table 6).

Withdrawals and dropouts

Sixteen patients (12 who were randomized to OIT and 4 randomized to CG at T0 who started OIT at T12) discontinued OIT because of DARs, one on PI and 15 on PII OIT buildup pattern ($P = 0.001$); two of them had passed the boiled egg DBPCFC at baseline. Eight were withdrawn by researchers because of their uncontrolled asthma (one on PI and 7 on PII), and 8 on buildup pattern PII dropped out due to the parent's decision ($P = 0.001$) (Figure 1 and Table 6).

3.2.2 | Safety data

Most of the patients who reached total desensitization (66/72, 91.66%) developed objective DARs during the buildup phase, 23/25 (92.00%) patients on PI vs 43/47 (91.48%) on PII; Mean DARs in PI patients 5.16 ± 3.61, median 5.00 (0-15), vs mean 5.15 ± 9.45, median 2.00 (0-56) in PII patients ($P > 0.05$). Most DARs were grade 1-2, and these reactions were more frequent with dose increments

TABLE 4 Dose adverse reactions (DARs) throughout the buildup phase, in patients reaching total desensitization: grades and associated factors

Buildup phase	Patients reaching total desensitization 57/64 (89.06%) had DARs 420 DARs/8448 doses	
	Mean ± SD	**Median (min-max)**
Total doses	108.60 ± 60.87	96.00 (7-329)
DARs	5.32 ± 7.91	3.00 (0-56)
Severe DARs (grade 4)	0.10 ± 0.37	0.00 (0-3)
Moderate DARs (grade 3)	1.17 ± 2.44	0.00 (0-14)
Mild DARs (grade 1-2)	3.97 ± 6.49	2.00 (0-46)
DARs associated with up-dosing	2.33 ± 3.00	1.00 (0-17)
DARs associated with exercise	0.12 ± 0.70	0.00 (0-6)
DARs associated with infections	0.33 ± 1.21	0.00 (0-9)

DARs, dose adverse reactions; grades 1-4, Sampson's grading[12]; up-dosing, incremented doses.

TABLE 5 Clinical characteristics and immunologic markers of the patients at the beginning of the OIT: patients following PI or PII buildup pattern (including patients randomized to the OIT group at inclusion and control patients who failed PEW DBPCFC at T12 and started OIT at that time)

	All patients who started PEW OIT N = 88				
	Pattern I N = 26		Pattern II N = 62		*P* value
Male/female rate	13M/13F		25M/37F		.273
Allergic asthma	10/26 (38.46%)		25/62 (40.32%)		.520
Atopic dermatitis	15/26 (57.69%)		40/62 (64.51%)		.082
Boiled egg tolerance at T0	5/26 (19.23%)		9/62 (14.51%)		.554
	Mean ± SD	**Median (Min–Max)**	**Mean ± SD**	**Median (Min–Max)**	
Age (months)	81.30 ± 13.51	83.50 (74–104)	82.51 ± 13.50	84.00 (72–109)	.430
Threshold response dose (PEW g proteins)	0.44 ± 0.52	0.22 (0.11–2.00)	0.57 ± 0.65	0.27 (0.11–1.88)	.396
EW SPT wheal mm	8.10 ± 2.61	8.50 (4.00–14.20)	8.41 ± 2.32	8.50 (4.00–13.49)	.490
EW sIgE (KU/L)	5.61 ± 7.20	2.90 (0.40–25.10)	13.81 ± 23.54	7.4 (0.2–227.0)	.007
OVA sIgE (KU/L)	3.52 ± 4.63	2.40 (0.20–18.62)	35.43 ± 179.90	4.7 (13.92–23.63)	.019
OVM sIgE (KU/L)	5.20 ± 6.17	1.80 (0.10–21.65)	19.40 ± 27.92	6.3 (0.1–121.2)	.016
EW sIgG4 mg/L	2.13 ± 4.26	0.46 (0.06–20.10)	1.11 ± 1.75	0.38 (0.04–7.86)	.082

OIT, oral immunotherapy; OIT CG, patients randomized to an egg-free diet at inclusion who falling PEW DBPCFC at T12 and started OIT at that time; Pattern I, buildup pattern with 30% weekly increments in the hospital plus 5% daily increments at home over the last tolerated dose. Pattern II, buildup pattern with 30% weekly increments in the hospital over the last tolerated dose and the same daily dose at home for a week, no extra daily increments; T0, inclusion and randomization time; PEW, pasteurized egg white; DBPCFC, double-blind placebo-controlled food challenge; SPT, skin prick test; weal (mm), perpendicular midpoint diameter (D[mm]+d[mm])/2)mm, subtracting the size of the saline weal; EW, egg white; OVA, ovalbumin; OVM, ovomucoid; sIgE, specific IgE antibody serum levels; sIgG4, specific IgG4 antibody serum levels.

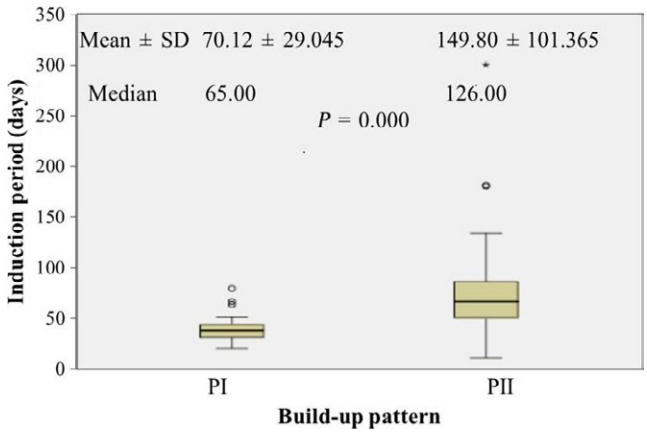

FIGURE 2 Comparison of induction periods, PI vs PII buildup patterns (*P* = 0.000). A general linear regression model (GLM) confirmed that the OIT patterns showed differences for the induction period adjusted by EW, OVA, and OVM sIgE antibody serum levels at baseline (*P* = 0.001). OIT: oral immunotherapy; PI: OIT buildup pattern with 30% weekly plus 5% daily increments over the last tolerated dose for a week; PII: OIT buildup pattern with 30% weekly increments and daily the last tolerated dose for a week; EW: egg white; OVA: ovalbumin; OVM: ovomucoid

and in PI patients (*P* < 0.05). However, grade 3-4 DARs occurred more often in the patients who followed PII buildup pattern (*P* < 0.05), and 1 patient on PI vs 6 on PII required adrenaline treatment (Table 6). No patients developed dysrhythmia and/or severe hypotension, hypovolemic shock, laryngeal edema, or respiratory or cardiac arrest.

4 | IMMUNOLOGIC MARKER EVOLUTION

Immunologic markers did not show significant changes in the control patients from T0 to T12. However, OIT patients who reached total desensitization showed a progressive decrease in EW SPT weal and EW, OVA, and OVM sIgE and a significant increase in EW sIgG4 serum antibody levels (*P* < 0.01). These changes did not show differences between PI and PII OIT patient groups (Figure 3).

5 | DISCUSSION

The current study is the largest multicenter, randomized controlled series of egg OIT reported to date. It is a homogeneous study in children (6-9 years) with persistent egg allergy, using pasteurized egg white equivalent to one medium-sized egg, to confirm effectiveness of OIT, analyzing the safety of this treatment. Our study randomized at inclusion 101 children with allergic reaction to PEW DBPCFC to OIT or an egg-free diet for 1 year (CG). Some 84.2% OIT patients reached total desensitization vs only 16.0% control patients who reached natural tolerance after 1 year on an egg-free diet. Despite the fact that control patients were younger and therefore they had more likely to develop natural tolerance. Our results are similar to those obtained by

TABLE 6 Effectiveness and safety of PI and PII OIT buildup patterns: total desensitization and DAR rate; induction period; total number of doses during the buildup phase (30% plus 5% up-dosing or daily maintained doses), total DARs, and their grades; and factors associated with DARs throughout the induction phase

	Patients starting OIT OIT patients at T0 (A or B) plus control egg allergic patients at T12 starting OIT N = 88				
	Pattern I N = 26		Pattern II N = 62		*P* value
Patients reaching total desensitization	25/26 (96.15%)		47/62 (75.80)		.01
Withdrawals/dropouts N= 16	1/26 (3.84%)		15/62 (24.19%)		.001
Dropouts by parents' decision	0/1		8/15		.001
Patients with dosing adverse reactions at induction period	23/25 (92.00%)		43/47 (91.48%)		1.00
	Mean ± SD	**Median (Min–Max)**	**Mean ± SD**	**Median (Min–Max)**	
Induction period (days)	70.12 ± 29.045	65.00 (27–154)	147.69 ± 101.34	126.00 (7–329)	.000
Total Doses build-up phase	69.23 ± 22.40	65.00 (27–154)	146.31 ± 99.34	125.00 (7–329)	.002
30% up-dosing	10.01 ± 2.02	9.00 (4–22)	20.90 ± 14,19	17.00 (1–47)	.028
5% up-dosing	59.34 ± 18.26	55.00 (23–136)	0	0	–
Total DARs	5.16 ± 3.61	5.00 (0–15)	5.15 ± 9.45	2.00 (0–56)	.053
Grade 3-4	0.88 ± 3.15	0.00 (0–16)	1.46 ± 2.36	0 .00 (0–9)	.031
Grade 1-2	4.88 ± 3.46	5.00 (0–15)	3.54 ± 7.80	1.00 (0–46)	.001
DARs associated with up-dosing	2.81 ± 2.74	2.00 (0–9)	2.09 ± 3.12	1.00 (0–17)	.122
DARs associated with exercise	0.04 ± 0.19	0.00 (0–1)	0.16 ± 0.85	0.00 (0–6)	.690
DARs associated with infections	0.73 ± 1.88	0.00 (0–9)	0.13 ± 0.59	0.00 (0–3)	.004

Pattern I: buildup pattern with 30% weekly increments in the hospital plus 5% daily increments at home over the last tolerated dose; Pattern II: buildup pattern with 30% weekly increments in the hospital over the last tolerated dose and the same daily dose at home per 1 wk; DARs: dose adverse reactions; OIT patients at T0: Patients randomized at T0 to OIT (A or B maintenance): OIT control patients at T12: Patients randomized to control group (CG) at T0 who did not pass PEW DBPCFC at T12 and then started OIT; Total desensitization: Children reaching 3.3 g protein PEW; Up-dosing: incremented doses; Grade 1, 2, 3, 4 reactions: Sampson grading.[12]

other researchers reporting 70%-90% success with total desensitization, equivalent to one whole raw egg or one raw egg white.[4,5,7,17-23]

Most of our patients (75%) developed reactions during the buildup phase, and 4.97% of the doses triggered reactions, median dosing reactions of 3.00 (0-56). This is in the lower range of reactions in the previously reported studies.[5–7,10,11,18,20–22,24–26] Most were mild reactions associated with up-dosing and less frequently with exercise or infections. Although seven patients required adrenaline treatment, no patients developed severe reactions.

We compared two OIT protocols (PI and PII) with different buildup patterns: Both included 30% weekly up-dosing in the hospital to ensure similar safety and compliance to protocol conditions. However, patients on the PI pattern were given 5% increment daily doses at home, whereas patients on PII maintained daily the last tolerated dose in the hospital during 1 week, until the target dose was reached. PI was significantly more effective and safe than PII OIT pattern (with a higher total desensitization rate of 96.2% vs 75.8%; a shorter induction period of 70.12 ± 29.04 vs 147.69 ± 101.34 days; and a lower withdrawal/dropout rate 1/26 (3.84%) vs 15/62 (24.19%), respectively). These differences between PI and PII could not be explained by differences in the material used for OIT, the target dose reached, the age of the population, the previous tolerance to cooked egg, the threshold egg dose response at baseline, or the association with asthma or other atopic diseases; all these factors were similar in PI and PII OIT patients. However, the patients in PII had higher EW, OVA, or OVM sIgE antibody serum levels at baseline, and these higher levels were more frequent in patients who did not reach total desensitization and in those with a longer induction period, although a general linear regression model (GLM) confirmed that the OIT pattern shows differences in the induction period adjusted by EW, OVA, and OVM sIgE antibody serum levels.

OIT has been demonstrated to be an effective treatment option to induce desensitization in patients with food allergy.[4–11,17–24,27–30] Previous randomized controlled studies using home-based protocols with various increment rates have reported lower total desensitization rates: Staden et al[6] reached 2.8 g protein of lyophilized hen's egg powder in 7 of 11 (48%) patients in a mean induction period of 7 months; Moriset et al[29] reached only 7 g of raw egg white (0.77 g proteins) after 6 months of treatment in 69.4% of patients. Dello Iacono et al,[18] with a similar protocol to our PI (slowly escalating doses of raw egg at home, alternating with dosage doubling in the hospital), achieved only partial desensitization in 90% of children (median EW sIgE 23.30 kU/L) over

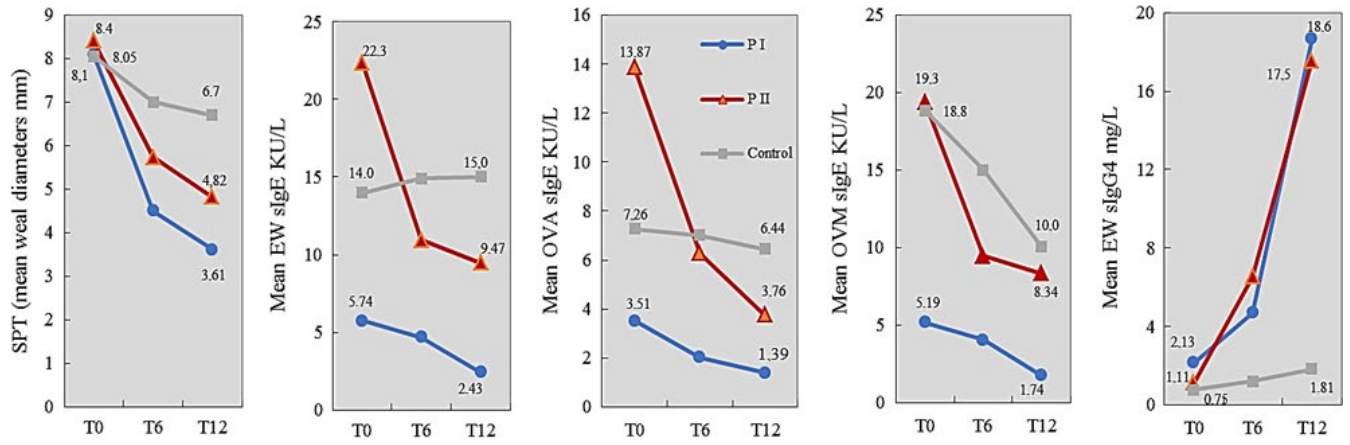

FIGURE 3 Evolution of immunologic markers from T0 to T12 in patients control and OIT patients reaching total desensitization (PI or PII buildup patterns): EW SPT mean weal diameters and (EW, OVA, and OVM) sIgE antibody serum levels showed a progressive decrease and EW sIgG4 antibody serum levels increased in the OIT group patients ($P < 0.01$). No differences were observed between PI and PII patients. These markers did not show significant changes in control patients. EW SPT: egg white (10 mg/mL) skin prick test; weal (mm): perpendicular midpoint diameter (D[mm]+d[mm])/2); EW: egg white; OVA: ovalbumin; OVM: ovomucoid. PI: buildup pattern OIT (30% weekly plus 5% daily increments over the last tolerated dose); PII: buildup pattern OIT (30% weekly increments and daily the last tolerated dose)

6 months, although our PI and PII patients showed lower median EW sIgE. Meglio et al,[27] using an OIT protocol with daily increments of raw hen's egg at home (9% during the first 80 days and 3.9% from then onwards), achieved total desensitization in 80% of children (median age 8.4 years, ovomucoid sIgE 6.8 kUA/L) with a duration of the desensitization protocol longer than 6 months. Their protocol resulted in a similar rate of desensitization, but the induction period was longer than our PII protocol with a similar OVM sIgE at the start of the OIT.

Like other studies, we observed a significant progressive decrease in EW SPT weal and egg sIgE in the patients who reached total desensitization.[5,10,11,18,25] EW sIgG4 at inclusion was lower in the control patients and in those who did not pass the boiled egg challenge; moreover, EW sIgG4 was increased at T12 in controls and in OIT patients, although this increment was significantly higher in OIT patients who reached total desensitization.[11,21,23,25] This higher increase is related to the high egg consumption in OIT patients and the small increase in control patients could be related to the egg cooked consumption by the control patients who passed the boiled egg challenge at T0 and to a lesser extent to the inadvertent egg exposure throughout the year of the study. No differences were found in the evolution of immunologic markers between patients who completed PI or PII OIT.

Most of our patients (75%) developed reactions during the buildup phase. The DAR rate in our study, 4.7% of doses, is in the lower part of the previously reported ranges.[5–7,10,11,18,20–22,24–26] The proportion of patients who developed adverse reactions was similar in both the PI and PII buildup patterns. The number of DARs (mean and median) was higher, but the reactions were milder in PI patients. These results could be conditioned by the greater number of up-dosing, overall 5% up-dosing, in PI patients. However, the total 30% weekly up-dosing was more numerous in PII patients, and they had more grade 3-4 reactions. Only one patient on PI (3.8%) required epinephrine treatment compared with 6 (9.1%) patients on PII. In addition, 16 patients (3.8% on PI vs 24.2% on PII) discontinued OIT during the induction period because of frequent and mainly moderate reactions and the adherence of patients to the OIT was lower with the PII pattern; 8/62 (12.90%) patients on PII withdrew from OIT due to the parents' decision, but none on PI. This could be explained by the fact that PII lasted longer than PI and patients on PII received more than 30% up-dosing and developed more grade 3-4 reactions. Like previous studies, frequent and moderate reactions were associated with higher egg sIgE serum antibody levels, minor threshold dose at baseline, allergic asthma, and discontinuation of OIT.[6,20,22] Vazquez et al[20] and Fuentes et al[21] reported a similar desensitization rate to the same target dose with a similar desensitization protocol to our PII, but they had a higher reaction rate (7.6%) and more patients requiring epinephrine treatment (26% and 20%, respectively). Meglio et al,[27] with a protocol ensuring constant daily increments (less than 10%), achieved a similar total desensitization rate (80%) in a longer induction period (more than 6 months) and they had a 70% rate of patients with adverse reactions, although they did not detail the severity of the reactions.

Our study confirms the effectiveness of OIT in children with persistent egg allergy, using pasteurized egg white with a target dose equivalent to a medium size egg. A buildup phase OIT of 30% weekly up-dosing in hospital plus 5% up-dosing at home was more effective and safer than the one with only 30% weekly up-dosing. This pattern would improve the adherence and the social and familial costs of the egg OIT. Nevertheless, these results should be confirmed in a randomized study of OIT designed to compare these buildup patterns.

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AUTHORS CONTRIBUTIONS

MMMF, PA, MP, EA, MA, and NS conceived and designed the study; MMMF, BMT, EA, ZL, FV, PM, PA, MC, MA, MC, BC, VB, MAM, GC, NS, GJM, and EL carried out the estudy and acquired the data; CMC analized the "in vitro" tests MMMF and MR carried out statistical analysis and interpreted the data; MMMF and EL wrote the manuscript; PA, MP, EA, MA, NS, MMMF, and EL critically revised the manuscript and supervised the study; and all the authors have read and approved the final manuscript. The authors attest to the veracity and completeness of the data and analysis as well as to the fidelity of the study to the protocol.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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