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Home-Based Oral Immunotherapy Protocol with Pasteurized Egg for Children Allergic to Hen's Egg

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ABSTRACT: **Background:** In the last decade the use of different types of oral immunotherapy for food-allergic patients has increased with generally satisfactory outcomes. Cow's milk and hen's egg, a common element in the daily diet, have received the main interest. Most of these immunotherapy regimens are performed in the hospital, causing inconvenience for both children and their parents.

Objectives: To assess the efficacy and safety of a home-based oral immunotherapy regimen with raw pasteurized egg.

Methods: The study group comprised children aged 6 years and older with allergy to hen's egg proteins, proven by positive skin prick-tests (SPT) and/or specific immunoglobulin E (sIgE) and positive open oral food challenge (OOFC) with boiled or raw egg. Patients who met the inclusion criteria and signed the informed consent form underwent egg immunotherapy according to an established schedule.

Results: The treatment was given to 31 of the 36 recruited patients: 80.6% of the intention-to-treat population achieved complete tolerance to the maximum dose equivalent to one raw hen's egg, 3.2% achieved incomplete tolerance, and 16.2% did not achieve an acceptable tolerance dose. Most of the latter patients had a positive baseline OOFC with low doses of boiled egg. The average number of reactions per treated patient was 5.8, most of them grades 1 and 2; there were no grade 4 reactions.

Conclusions: This home-based oral immunotherapy protocol proved to effectively induce tolerance to hen's egg in most of the egg-allergic children and its safety profile was acceptable.

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KEY WORDS: oral immunotherapy, hen's egg, food allergy, desensitization

Although there are few reports in the literature before the 1980s of specific oral tolerance induction, it was the publication by Patriarca et al. [1] that boosted the use of SOTI protocols in food-allergic patients, mainly children. While most of the reported protocols focused on cow's milk and hen's egg since these are ubiquitous foods in the regular diet, researchers around the world have reported successful SOTI with other foods such as fish, wheat, vegetables, and peanut [see Ref. 2 for a review].

Most of these regimens include weekly dose increases in the hospital setting, with dose maintenance during the week, taking from 12 to 24 weeks (or even more) to reach the final dose. Recently, schedules with a duration of only a few days have been introduced but they require that the treated patient be admitted to the hospital or at least attend the hospital daily.

Based on the SOTI regimens published by Patriarca et al. in 1998 [1], our group designed a shortened home-based oral immunotherapy protocol (CLOJ/01-2004) with cow's milk for milk-allergic children, and during 2004–2008 we conducted a clinical trial to assess its efficacy and safety. In summary, this protocol included 24 treated patients who achieved a complete or partial tolerance (over 100 ml of cow's milk); namely, a rate of 95.8%, with an average of 3.6 reactions per patient, most of them mild to moderate, and no severe reactions necessitating injection of epinephrine [3]. Since then, our clinic offers this treatment as part of our services.

Egg allergy is somewhat different from allergy to milk in that there are two distinct populations of egg-allergic children: those tolerating cooked egg but not raw egg, and those not tolerating either. In daily clinical practice, we consider that egg-allergic patients have outgrown their allergy when they tolerate sufficient amounts of raw egg to follow a normal unrestricted diet. Based on our previous results with milk, we designed another study protocol (CLOJ/01-2009) to assess the safety and efficacy of a home-based SOTI with raw pasteurized egg in egg-allergic children.

PATIENTS AND METHODS

The study protocol was approved by the local ethics committee and verbal and written information was provided to the parents/guardians before their children entered the study. Informed consent was obtained for both the diagnostic tests and the SOTI regimen.

STUDY POPULATION

The inclusion criteria were children aged 6 years and older with a history of a clinical reaction when eating egg (either

SOTI = specific oral tolerance induction

cooked or raw), positive skin-prick tests and/or specific serum immunoglobulin E to any of the tested egg extracts (see below), and a positive open food challenge test with either cooked or raw egg.

The exclusion criteria were age ≤ 5 years, negative SPT and sIgE to egg fractions, tolerance to foods containing raw egg in sufficient amounts to be able to follow a normal free diet, negative food challenge with raw egg, grade 4 anaphylaxis based on European Academy of Allergy and Clinical Immunology criteria [4], egg-related clinical entities without an IgE-mediated pathogenesis, chronic medications that interfere with the test results, and lack of informed consent from the parents or guardians.

DIAGNOSTIC TESTS

An allergy history was taken to gather information about previous reactions to egg (and other foods), a personal or family history of other allergic diseases, and the use of concomitant medications. SPTs were carried out on the anterior area of the forearm with newly prepared extracts of egg white, egg yolk, ovalbumin, ovomucoid, and lysozyme (Diater Laboratories, Madrid, Spain). A result was considered positive if the wheal diameter was > 3 mm (provided that the saline control was negative). Immunological determinations were done at baseline, end-of-treatment, at 6 months and at 18 months, but are not commented on in this article.

An OFC with cooked egg (one boiled hen's egg as is, or mixed in a vegetable purée) was carried out if the child was following a strict egg-avoidance diet. The OOFC with pasteurized raw egg (mixed with yogurt or fruit juice) was performed if the child was already tolerating cooked egg in his/her diet or if the first challenge test with cooked egg had been negative. Children achieving tolerance to the complete or to a sufficient amount of pasteurized egg with the SOTI regimen were then submitted to a final OOFC with natural raw egg to verify that achieving tolerance to pasteurized egg assured tolerance to natural raw egg. A test was considered positive when symptoms and objective signs occurred upon egg ingestion, precluding the administration of medication to control the reaction. All food challenges were done at the hospital and close to the intensive care unit.

STUDY ARMS

Upon completing all the diagnostic tests, the children (and their parents) were advised to follow the SOTI regimen. Those who agreed (and signed the informed consent) were assigned to the treatment group, and those who did not want to participate were assigned to the control group (these patients were followed at 6 and 18 months, and the in vivo and in vitro allergy tests were repeated). For ethical reasons, this allocation was not done in a random manner and was based solely on the children's and parents' decision. Children whose food challenge test with raw egg was negative (i.e., they tolerated a complete natural raw egg) were excluded from the study since this indicated that they had outgrown their egg allergy naturally.

SOTI REGIMEN

Specific oral tolerance induction to pasteurized egg was performed according to the designed protocol [Table 1]. The patients received their first treatment dose (with diluted pasteurized egg) at our clinic, the first dose of the undiluted solution, the dose equivalent to the one that was positive on the food challenge, and the final dose (50 ml). At their first treatment visit, the parents were given verbal and written information about the dose schedule, possible reactions and how to manage them, and a 24 hour phone number for contacting one of the study investigators if necessary. The remaining doses were administered at the patient's home, but the patients could come to the clinic whenever they felt it necessary or if they felt insecure. All patients were pretreated with cetirizine (0.25 mg/kg of weight/day), which was continued until the end of treatment. Other medications (such as cetirizine given twice daily, inhaled budesonide, oral sodium cromoglicate, or oral corticosteroids) were added during the treatment course according to the investigators' clinical judgment).

The product used for the treatment was complete (white and yolk) pasteurized egg (PITAS, Madrid, Spain). Approximately 45 ml of pasteurized egg equals one natural egg: protein content 11.5 g/100 g of the product. Before undertaking the study, in vitro studies were performed with an extract of the raw product and an extract of the natural raw egg to assess the product's allergenicity by means of immunoblotting and enzyme-linked immunosorbent assay inhibition tests with a sample of pooled sera from the egg-allergic patients.

All adverse events were registered and classified as follows: AE1 = atypical symptoms for an allergic reaction and not representing a risk to the patient's life, AE2 = symptoms typical of an allergic reaction and classified as mild according to the EACCI classification [4], AE3 = moderate symptoms typical of an allergic reaction, AE4 = severe symptoms typical of an allergic reaction. Moreover, each adverse event was categorized as CR (**c**learly related to the treatment dose), PR (**p**robably related), PoR (**p**ossibly related) and NR (**n**ot related), depending on the time elapsed since taking the dose, the time the symptoms occurred, and the presence of other concurrent factors (such as another disease, ingestion of other foods to which the patient was allergic to, etc.). The

SPT = skin-prick test
sIgE = specific serum immunoglobulin E
OFC = oral food challenge
OOFC = open oral food challenge

AE = adverse events
EACCI = European Academy of Allergy and Clinical Immunology

Table 1. SOTI regimen with liquid pasteurized egg*

Initial dilution (1/40): 0.5 ml of the solution in 19.5 ml of purified water = 3.01875 mg of egg protein/ml of the solution

Days	No. of drops	Solution (ml)	Pasteurized egg (mg)	Egg protein (mg)	x fold increase
1	1	0.05	1.291	0.151	
2	1	0.05	1.291	0.151	1
3	2	0.1	2.582	0.302	2
4	2	0.1	2.582	0.302	1
5	5	0.25	6.455	0.755	2.5
6	5	0.25	6.455	0.755	1
7	10	0.5	12.910	1.509	2
8	10	0.5	12.910	1.509	1
9	20	1	25.820	3.019	2
10	20	1	25.820	3.019	1
11		2	51.640	6.038	2
12		2	51.640	6.038	1
13		5	129.100	15.094	2.5
14		5	129.100	15.094	1
15		10	258.200	30.188	2
16		10	258.200	30.188	1
17		20	516.400	60.375	2
18		20	516.400	60.375	1
19		40	1032.800	120.750	2
20		40	1032.800	120.750	1

Continuation solution (dilution 1/1): 1 ml = 120.75 mg of egg proteins

Days	Solution (ml)	Pasteurized egg (mg)	Egg protein (mg)	x fold increase
21	1	1033.0	120.75	
22	2	2066.0	241.50	2.00
23	3	3099.0	362.25	1.50
24	4	4132.0	483.00	1.33
25	5	5165.0	603.75	1.25
26	6	6198.0	724.50	1.20
27	7	7231.0	845.25	1.17
28	8	8264.0	966.00	1.14
29	9	9297.0	1086.75	1.13
30	10	10,330.0	1207.50	1.11
31	12	12,396.0	1449.00	1.20
32	15	15,495.0	1811.25	1.25
33	20	20,660.0	2415.00	1.33
34	25	25,825.0	3018.75	1.25
35	30	30,990.0	3622.50	1.20
36	40	41,320.0	4830.00	1.33
37	50	51,650.0	6037.50	1.25

*1 ml of pasteurized egg = 0.12075 g of egg proteins
50 ml of pasteurized egg = 1.16 medium-size whole egg

NR category only included those reactions clearly related to the ingestion of an offending food other than egg.

STATISTICAL ANALYSIS

Descriptive statistics were used for the demographic data. For the comparison between the baseline and post-treatment data of the wheal diameters, sIgE and sIgG4, the two-tailed Wilcoxon's test for paired samples (level of significance $P < 0.05$) was employed, using GraphPad Instant 3 statistical software.

RESULTS

The demographics of the study population, subcategorized as treatment group (31/36), control group (patients not wanting the treatment, 3/36), and patients withdrawn from the study (because of negative challenge tests, 2/36) are shown in Table 2. The mean age of the patients, 17 females and 18 males, was 9.6 years (range 6–15 years).

EFFICACY RESULTS

Slightly over 80% of the treated patients (25/31) achieved complete tolerance to the maximum dose of the regimen (50 ml of pasteurized egg), 3.2% (1/31) achieved partial tolerance, 9.7% (3/31) did not achieve tolerance to sufficient amounts of pasteurized egg to follow a normal diet but increased their reactivity threshold at the final food challenge as compared with the baseline challenge test, and 6.5% (2/31) did not achieve tolerance or increase their reactivity threshold. The median times of the treatment (time frame from the first to the last treatment dose) for the whole treatment group and the subgroup achieving complete tolerance were, respectively, 43 and 43 days (minimum 37 and 37 days, maximum 85 and 70 days; the pre-established treatment duration was 37 days). Of nine patients who were already tolerating cooked egg at baseline, eight achieved complete tolerance and one did not want the treatment and was allocated to the control group. In the subgroup of patients whose baseline OOFC with cooked egg was positive, those showing a reactivity threshold at less than one-fourth of egg did not achieve a minimum acceptable tolerance and they had to be withdrawn because of repeated severe reactions.

Of the 25 patients achieving complete tolerance, 23 also tolerated – without any reaction – the post-treatment food challenge test with one natural raw egg. Besides allowing them to eat any form of cooked egg, these patients were

Table 2. Patients' demographics and study arms distribution and outcomes

Pt. #	Age (yrs)	Gender	Allergic history	Baseline OVA-specific IgE	Baseline OVM-specific IgE	Distribution*	Final SOTI outcome	Pt. #	Age (yrs)	Gender	Allergic history	Baseline OVA-specific IgE	Baseline OVM-specific IgE	Distribution*	Final SOTI outcome
1	9	F	Pos	2.69	5.23	TG	NTIT	19	8	M	Pos	3.06	2.59	TG	CT
2	11	M	Pos	3.63	9.6	TG	NTWC	20	7	F	Pos	0.29	0.35	CG	ND
3	9	F	Pos	0.86	2.24	TG	CT	21	8	F	Pos	0.84	0.89	CG	ND
4	9	M	Pos	3.46	6.56	TG	CT	22	6	F	Pos	8.21	12.4	CG	ND
5	8	M	Pos	1.48	0.81	TG	CT	23	12	F	Pos	3.44	5.73	TG	CT
6	9	M	Pos	3.99	6.01	TG	CT	24	15	M	Pos	4.92	7.54	TG	CT
7	8	F	Pos	31.3	32.2	TG	NTIT	25	7	M	Pos	0.12	2.17	TG	CT
8	9	M	Pos	0.14	0.77	WD	ND	26	14	M	Pos	0.63	5.75	TG	CT
9	8	M	Neg	5.35	3.93	TG	CT	27	14	F	Pos	0.32	5.2	TG	CT
10	15	M	Pos	43.1	46.5	TG	NTIT	28	7	F	Pos	6.94	6.07	TG	PT
11	9	F	Neg	2.44	0.6	TG	CT	29	11	M	Pos	6.64	10.9	TG	CT
12	11	F	Neg	1.98	1.9	TG	CT	30	10	M	Pos	0.69	0.66	TG	CT
13	6	M	Pos	› 100	› 100	TG	NTWC	31	10	F	Pos	0.51	3.2	WD	ND
14	12	M	Neg	3.25	0.25	TG	CT	32	13	F	Pos	1.09	1.17	TG	CT
15	10	M	Pos	3.61	5.9	TG	CT	33	9	F	Pos	2.49	2.56	TG	CT
16	8	F	Pos	5.73	6.21	TG	CT	34	14	M	Neg	6.73	6.22	TG	CT
17	7	M	Pos	8.37	8.63	TG	CT	35	9	F	Pos	0.14	0.32	TG	CT
18	6	F	Pos	13.1	13.1	TG	CT	36	7	M	Pos	21.8	33.1	TG	CT

*Two patients were excluded from the study because of baseline negative oral food challenge test with raw egg

M = male, F = female, OVA = ovalbumin, OVM = ovomucoid, Pos = positive, Neg = negative, TG = treatment group, CG = control group, WD = withdrawn, CT = complete tolerance, PT = partial tolerance, NTIT = no tolerance but with increased reactivity threshold, NTWC = no tolerance without change in the reactivity threshold, ND = not done

instructed to eat one-half of a natural raw egg mixed with yoghurt or fruit juice at least three times a week until the next follow-up visit in order to maintain the acquired tolerance. The remaining two patients who had mild reactions with natural raw egg, as well as the patient achieving partial tolerance, were instructed to eat any form of cooked egg as well as foods containing partially uncooked egg and small amounts of raw egg (e.g., omelette, fried egg, mayonnaise, etc.).

TOLERABILITY RESULTS

The distribution of reactions by severity, degree of causality, and type of symptoms is shown in Table 3. In total, there were 180 adverse events. Of the 31 treated patients, 8 (25.8%) did not experience any kind of adverse events during the treatment course. However, one patient experienced 23 AEs. The mean number of AEs per treated patient was 5.8.

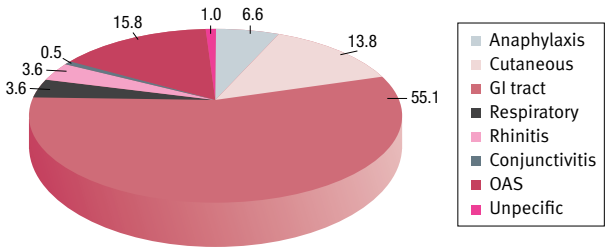
As shown in Figure 1, more than half the reactions involved the gastrointestinal tract, ranging from light abdominal pain after the dose intake to severe and prolonged abdominal pain and abrupt diarrhea or vomiting. Gastrointestinal symptoms can occur from several minutes to several hours (up to 9) after the dose intake. Cutaneous (itching or urticaria) symptoms and oral allergy syndrome were also reported relatively often (13.8% and 15.8%, respectively). Anaphylaxis was considered when three different organ systems were affected, or two organ systems but with moderate to severe symptoms. In four cases (0.02%), auto-injectable adrenaline was used at the patient's home to treat the adverse reaction.

Table 3. Distribution of the adverse events by severity and degree of causality

Severity	No. (%)
AE1	8 (4.4)
AE2	147 (81.7)
AE3	25 (13.9)
AE4	0 (0)
Degree of causality	
Clearly related	145 (80.6)
Probably related	17 (9.4)
Possibly related	14 (7.8)
Not related	4 (2.2)

See Patients and Methods for the classification criteria

Figure 1. Relative distribution of the organ systems involved in the 180 adverse reactions registered with the SOTI regimen



OAS = oral allergy syndrome

DISCUSSION

Despite isolated reports of tolerance induction to foods in food-allergic patients, the publication in 1998 by Patriarca et al. [1] of their experience using SOTI regimens with several foods is notable and will boost the use of this type of therapy in food-allergic individuals, at least in our country.

In Spain, the first SOTI protocols were carried out with cow's milk. In general, this protocol is performed in allergy units of the Public Health Care system and rarely in private facilities, our clinic being one of the few private allergy centers conducting this kind of clinical study to assess the effectiveness and safety of this treatment before offering it to patients. In general, the Spanish experience using the SOTI regimens with cow's milk is extensive and has yielded fairly good results, with reported complete tolerance rates > 90%, depending on the population studied [3,5,6]. Even severely allergic children have been included with promising results, although extreme care has to be taken [7]. In most of the studies, the patients were 5 years of age and older, since the evidence shows that rarely does a child allergic to cow's milk spontaneously outgrow his/her allergy [8]. There is, however, an interesting national multicenter study promoted by the Spanish Society of Pediatric Allergy that compared the tolerance acquisition rates in two groups of milk-allergic children aged 2–3 years [9]. The study comprised 60 patients randomly allocated to a long SOTI regimen with milk or to the control group (not treated). The results clearly demonstrated that SOTI induced complete tolerance to milk in more patients within this age range than did expectant management [10].

In recent years, more groups have instituted SOTI protocols with hen's egg for egg-allergic children [11-13]. Again, in Spain most of these protocols were performed in the Public Health Care system, with fairly good results regarding efficacy and acceptable safety results depending on the severity of the patients' egg allergy and the fact that tolerance induction to egg seems to be somewhat more difficult than to milk [14,15].

There is, however, higher variability among these protocols not only in the schedules but also in the type of product used to achieve desensitisation: natural boiled egg, well-cooked French omelette, lyophilized egg white, pasteurized egg white, and pasteurized whole egg. In our case, the rationale for using pasteurized whole egg was that in inducing tolerance to egg, we wanted to achieve tolerance to the whole product, as occurs in patients acquiring the tolerance by themselves. The other reason for using fresh liquid pasteurized egg is that the pasteurizing process assures the elimination of Salmonella and other contaminating bacteria without altering the structure of the egg proteins, since the product remains in a liquid state and not in a solid state that would occur in the case of heat-induced protein coagulation. In order to verify this, before starting the trial we assessed the allergenicity of an extract of crude egg and an extract of liquid pasteurized egg by means of SDS-PAGE immunoblotting with a sample of pooled sera from egg-allergic patients, as well as an ELISA-inhibition assay. The pattern of protein recognition by specific IgE contained in the pooled sera sample was almost identical for both extracts, but the ELISA-inhibition assay showed that the natural crude egg extract was about four times more allergenic than the pasteurized extract (data not shown). However, the final food challenge test with one natural raw egg in the patients reaching the maximum dose of the SOTI regimen (50 ml) showed that this higher in vitro allergenicity of crude egg versus pasteurized egg is not clinically relevant, since all patients achieving tolerance to 50 ml of pasteurized egg also tolerated one raw egg.

Our study shows that tolerance to raw egg can be induced by using a SOTI regimen with liquid pasteurized egg in egg-allergic children. There are three clear patterns of response to the SOTI regimen:

- in patients already tolerating cooked egg, the probability of achieving complete tolerance to raw egg is very high and relatively easy (5 of the 8 patients having a negative OFCT with boiled egg had no reactions throughout the SOTI regimen, one had one reaction, and of the remaining 2 one had 11 mild reactions and the other had 11 reactions, 3 of them anaphylaxis)
- in patients reacting to a low dose of boiled egg at the baseline OFC, the likelihood of achieving a change in their reactivity to egg after the SOTI regimen is very low; we do not offer this therapy to these patients because the predictable outcome is not worth the suffering
- in patients in the "grey zone," who react to intermediate to high doses of cooked egg at the baseline OFC, the probability of achieving complete tolerance to raw egg is high but very likely to have adverse reactions during the treatment course (only 3 of the 23 patients having a positive baseline OFC with cooked egg had no reactions at all during the SOTI regimen).

ELISA = enzyme-linked immunosorbent assay

With regard to the safety of our SOTI regimen, inducing tolerance to egg is more complicated than for cow's milk: the percentage of patients experiencing at least one adverse reaction during the treatment is high (about two-thirds of the patients), with a mean number of reactions per patient of almost 6, and the reactions are somewhat more severe (no patient needed adrenaline in our previous protocol with milk, versus four patients in the protocol with egg). Also, more than half the reactions involved the gastrointestinal tract with the particularity that these reactions could have a delayed onset (in one case, even 9 hours after the dose intake) and took longer to resolve than those affecting other organs. It is paramount, therefore, to explain these facts to the patients and parents and provide them with a telephone number that they can call around the clock to receive instructions if needed.

CONCLUSIONS

We report the efficacy and tolerability outcomes of a home-based SOTI regimen with liquid pasteurized egg in egg-allergic children. The results show fairly good tolerance rates, allowing us to include this therapy in our services portfolio. However, this treatment has to be given in well-selected patients and under close supervision (regular follow-up visits and 24 hour phone service) by a specially trained allergist.

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