

ORIGINAL ARTICLE

Oral rush desensitization to egg: efficacy and safety

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Summary

Background Current management of egg allergy relies on egg elimination from the diet. It does not protect patients from reactions after accidental ingestion of the food and it has a negative influence on quality of life. To solve these problems, some desensitization protocols have been described that are safe and effective, but only one study of a rush regimen for egg with a small patient sample has been published.

Objective To evaluate the safety, efficacy and immunologic effects of an oral rush desensitization protocol for immediate egg allergy.

Methods Subjects aged 5 years or older with symptomatic IgE-mediated allergy to hen's egg underwent a 5-day oral tolerance induction regimen and were subsequently maintained on a regular egg intake. The variables studied were the reactions that occurred during the induction regimen and follow-up and the duration of desensitization. Prick test weal size and egg white-specific IgE and IgG concentrations were monitored.

Results Twenty-three patients between 5 and 17 years of age entered the protocol. Twenty (86.9%) achieved the daily intake of a whole cooked egg, 14 of them within the scheduled 5 days. One abandoned the protocol and two were changed to a slower regimen because of repeated reactions. Allergic reactions were frequent but in general were mild. No severe reactions occurred. During follow-up of at least 6 months, egg was well tolerated by all patients. Compared with baseline, skin prick test weal size and egg white-sIgE levels had fallen at 3 months, although the differences were only significant at 6 months.

Conclusions and Clinical Relevance The rush protocol described is useful and safe for achieving tolerance to egg within a few days but it should always be performed in a highly supervised setting. A high proportion of patients allergic to egg can effectively be desensitized using the described schedule, with the advantage of shortening the time to become protected from reactions after inadvertent ingestion of egg, with no increase in the risk compared with the earlier reported slower protocols.

Keywords egg allergy, egg immunotherapy, oral rush desensitization, specific oral tolerance induction

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Introduction

Hen's egg is one of the main causes of food allergy in children under 3 years of age in Europe. The prevalence of egg allergy varies depending on the study; data from a meta-analysis [1] reported figures between 0.5% and 2.5% in pre-schoolchildren considered to be allergic based on the clinical history, the results of skin prick tests (SPT) and specific IgE (sIgE) levels. The prevalence has never exceeded 1% in studies performed in children over 5 years of age or in adults, suggesting a natural progression of the disorder towards tolerance. The largest prospective study

published, with a cohort of 53 children, reported the onset of tolerance in 50% of cases by 4–4.5 years of age [2]; however, there are more recent studies that suggest that tolerance develops later, although this may be due to the inclusion of a more atopic population [3]. In any case, allergy persists in a significant proportion of patients after 5 years of age [4, 5].

Until a few years ago, the only possible intervention for food allergy was avoidance of the food, but this does not adequately resolve the problem, as the affected population remains at risk of sometimes serious reactions after accidental ingestion of the food [6]. Furthermore, the

constant attention required to avoid egg, a food that is so widely used, and the fear of possible reactions, lead to a substantial decrease in the health-related quality of life of both the patients and their families.

Previous experience has shown oral tolerance induction or desensitization to various foods to be the only method to modify the natural course of allergy, or at least, to avoid reactions after inadvertent ingestion [7–14]. The proposed regimens consist of the administration of increasing doses of the food orally until a normal portion is tolerated, or at least, until a sufficient quantity is tolerated to protect against accidental intake. After desensitization, the food must be eaten regularly to maintain tolerance.

Modification of the clinical response to egg ingestion after the regimens described above usually leads to parallel immunological changes. In most cases, there are changes similar to those that occur after conventional immunotherapy with aeroallergens, that is, a fall in the sIgE and a rise in the specific IgG (sIgG) [13–16].

The desensitization regimens published in the literature have usually been performed over periods of weeks or months. Most of these protocols have been found to be safe and effective, and between 52% and 90% of children achieve the above-mentioned objectives [7–17].

Recently, rush protocols have been reported for cow's milk and other foods; those protocols have a 1-week induction phase [18–22]. The largest series are published by Staden *et al.* [18] and Martorell *et al.* [21], with nine and four children, respectively; desensitization to cow's milk was successful in 3–7 days in 66–75% of cases; tolerance to protective doses was achieved in all the children. The reactions that occurred during the procedures were always mild. These regimens gave patients a crucial advantage by significantly bringing forward the moment at which they were protected from potentially severe allergic reactions, with no apparent increase in the risk compared with earlier protocols. As far as we have been able to ascertain, only one oral rush desensitization protocol with few patients has been published for egg [23].

We performed a study to evaluate the safety and efficacy of a new protocol for rush desensitization to egg designed for children over 5 years of age with IgE-mediated egg allergy. We also evaluated the immunological changes detected during the follow-up.

Methods

Study design

This was a prospective, open, uncontrolled study.

Patient selection

The patients recruited for inclusion in the protocol were children over 5 years of age seen in the Allergy Depart-

ment of Ciudad Real General Hospital and diagnosed with symptomatic IgE-mediated egg allergy. The study was approved by the hospital ethics committee.

Inclusion criteria. Children over 5 years of age who satisfied all the following criteria were included:

- A history suggestive of immediate allergy to egg (urticaria, angioedema, vomiting, diarrhoea, rhinitis, dyspnoea or hypotension within the first 2 h after eating egg).
- IgE-mediated egg allergy demonstrated by at least one of the following tests:
 - (a) Positive SPT to egg or its proteins (weal diameter 3 mm larger than that of the normal saline control). The allergens used were pasteurized raw egg white and commercial extracts of egg, egg white, ovalbumin and ovomucoid supplied by LETI Laboratories (Barcelona, Spain).
 - (b) Detection of serum sIgE (>0.35 kU/L) to egg white or any of its proteins (ovalbumin, ovomucoid, lysozyme and conalbumin), measured by fluorescence enzyme immunoassay (Phadia, CAP System, Uppsala, Sweden).
 - (c) Positive oral challenge test to egg or an unequivocal history of a reaction to egg in the previous 3 months. Oral challenges were performed with cooked whole egg and raw egg white according to the recommendations of the position paper of the European Academy of Allergology and Clinical Immunology [24] and in an open manner. When subjective symptoms were triggered (oral pruritus, abdominal discomfort), the challenge tests were blinded.
- Informed consent form signed by the father, mother or legal guardian.

Oral challenge tests were not performed when the mean weal diameter or the sIgE to egg white was equal to or exceeded 13 mm [25] or 7 kU/L [26], respectively, unless there was any doubt about the reaction suffered by the patient.

Exclusion criteria. Patients who were unstable from a respiratory point of view or who presented intercurrent disease at the time of starting desensitization were excluded.

Desensitization protocol

The desensitization protocol was performed at the Allergy Day Unit of the Ciudad Real General Hospital, under the direct supervision of the medical and nursing staff, and with full cardiopulmonary resuscitation measures available for the treatment of possible allergic reactions that could occur during the procedure. A paediatric intensive care unit was available at the hospital.

Patients were not admitted, but remained under observation for 7 h each day, with the possibility for increasing this period if required.

Desensitization was performed using pasteurized raw egg white mixed with a food product well tolerated by the patient (yoghurt, milkshake). According to information supplied by the manufacturer, the egg white had been pasteurized by heating to 57 °C for 4.25 min in order to reduce contamination by microorganisms without destroying the proteins. Oral administration of pasteurized egg was programmed as described in Table 1.

When the desensitization lasted more than 5 days, parents were instructed to administer the last tolerated dose of egg white at home each day over the weekend.

Desensitization was considered to have been achieved when the patient tolerated one whole cooked egg and 8 mL of raw egg white (one egg = 30 mL of egg white). A slow regimen was proposed in those patients who suffered repeated moderate reactions or any severe reaction to a given dose; that regimen involved a weekly increase of 0.5 mL in the dose from the last tolerated dose of egg white.

SPT with the allergens listed above was performed on all patients before starting desensitization, and the tests were repeated at 3, 6 and 12 months. Blood tests were also performed to measure sIgE and sIgG before desensitization, at 3 weeks and at 3, 6 and 12 months.

Reactions that occurred during the desensitization protocol were classified according to the categories proposed by Perry et al. [27]: mild reactions were those limited to oral or skin symptoms; severe reactions included cardiovascular or respiratory symptoms or involvement of any four systems; all other reactions were classified as moderate, although we considered isolated abdominal discomfort as mild when it lasted for 30 min or less.

Table 1. Desensitization protocol

Day	Time interval	Egg white (mL)	Equivalent egg-white powder (mg)
1	1 h	0.001	0.13
		0.005	0.65
		0.01	1.3
		0.05	6.5
2	1 h	0.1	13
		0.2	26
		0.5	65
		1	130
3	2.5 h	2	260
		4	530
4		6	795
5	2 h	8	1060
	30 min	Half a cooked egg	2000
		Half a cooked egg	2000

The protocol was individualized according to each patient's tolerance to egg:

- Mild allergic reactions were to be treated when necessary and the regimen was to be continued when the patient became asymptomatic.
- Moderate reactions were to be treated and desensitization would be restarted on the following day at the previously tolerated dose.
- Severe reactions were to be treated with the necessary measures and in the appropriate department, followed by an assessment of whether to interrupt desensitization or reduce the dose on the following day to 1/10 of the dose that caused the reaction.

Patient follow-up. As there have been reports of loss of tolerance within 48 h after elimination of the food from the diet, patients who achieved tolerance to a whole egg continued with daily ingestion of a cooked egg for the first 3 months [17]. They were allowed to eat any food containing egg in lesser quantities. At 3 months, they were told to space out exposure to every 48 h and at 6 months to every 72 h. Tolerance to these intervals of egg avoidance was monitored in the hospital.

The patients' parents were instructed verbally and in writing about the recommendations to be followed after desensitization and how to treat possible allergic reactions. They were also given a direct telephone line for consultation. Patients were told not to perform physical exercise [28, 29] for 2 h after eating egg and not to take non-steroidal anti-inflammatory drugs for 3 h before or after ingestion. No special recommendations were given for viral infections.

Variables measured. The following variables were measured in each patient:

- Number and severity of adverse reactions occurring after oral exposure to egg during the desensitization and follow-up phases.
- Minimum dose of egg white that triggered symptoms during the desensitization protocols or challenge tests.
- Days until tolerance to a whole cooked egg was achieved, excluding weekends.
- SPT weal size and levels of sIgE and sIgG before desensitization and during follow-up.

Statistical analysis. The data from each patient were gathered in a case report form in order to enable detailed and systematic data collection. The SPSS version 15.0 statistical package (SPSS Inc., Chicago, IL, USA) was used for the statistical analysis.

Descriptive statistics of the variables including means, standard deviations and frequencies were computed. The

concentrations of egg-sIgE and sIgG and the mean size of the weal at the different study time-points were compared with their baseline values using the one-sample paired *t*-test or the Wilcoxon's test, after verifying the distribution of the difference between data using the Shapiro-Wilk test. The *t*-test or Mann-Whitney test was used to compare different groups.

Differences were considered significant when $P < 0.05$.

Results

Twenty-three patients (six girls and 17 boys) aged between 5 and 17 years (mean, 8.1 years) were included in the protocol. Fourteen patients had atopic dermatitis and 15 had allergic asthma. Twelve of the 23 patients reacted to their first egg intake. The diagnosis of symptomatic egg allergy was made in 12 patients by means of a controlled oral challenge test. Patients no. 1 and 2 did not present a clear history of egg allergy (perioral erythema with the first ingestion of egg white) and were therefore challenged despite having a positive SPT or higher sIgE levels than the established cut-off point. Anaphylaxis was triggered in both cases by the oral challenge test, performed 10 days before starting the desensitization protocol in one patient

and 3 months before in the other. Patient no. 7 was not challenged as he had developed an unequivocal reaction to egg 2 months before starting the desensitization programme (Table 2).

Twenty (86.9%) of the 23 patients in the study achieved tolerance to a whole cooked egg (omelette) with our protocol, 14 of them within the programmed 5 days and six in < 10 days.

One patient, a 14-year-old boy with allergic asthma and sIgE to egg white > 100 kU/L, abandoned the desensitization due to repeated reactions with the same dose of egg white, although the reactions were generally mild (abdominal pain with or without vomiting). He had no history of anaphylaxis but had presented vomiting and diarrhoea a few minutes after eating an ice cream.

Two patients were switched to a slow protocol and achieved tolerance in 60 and 80 days. One of them presented a previous history of anaphylaxis to egg and the other had rhinoconjunctivitis and vomiting after a challenge test with egg white; they did not show more intense SPTs or higher levels of sIgE to egg white than the group that completed rush desensitization. Significant differences were detected in these variables between patients who could be desensitized in 5 days and those

Table 2. Subject demographics at enrollment and anamnesis on egg exposure

Patient no	Age (years)	Sex	AD	Asthma	sIgE (kU/L)*	SPT (mm) [†]	ChT [‡]	Symptoms before egg desensitization
1	5	F	Yes	Yes	19.2	12.5	+	Anaphylaxis (challenge test)
2	8	M	No	No	8.21	9.5	+	Anaphylaxis
3	6	F	No	No	0.93	10	+	Urticaria, angioedema
4	6	M	No	Yes	1.73	6.5	+	Cough, abdominal pain
5	9	M	Yes	Yes	1.47	13	ND	Urticaria, angioedema, diarrhoea
6	9	M	Yes	Yes	7.5	9.5	+	Rhino-conjunctivitis, oral pruritus, vomiting
7	6	M	No	No	1.3	7	ND	Cutaneous rash, chest tightness (2 months before)
8	6	M	Yes	Yes	28.1	7	ND	Cutaneous rash
9	17	F	Yes	Yes	11.5	10.5	ND	Urticaria, angioedema, vomiting, asthma
10	7	M	Yes	Yes	4.31	9	ND	Urticaria, vomiting
11	8	M	Yes	Yes	0	4.5	+	Palpebral angioedema
12	14	M	Yes	No	1.1	12.5	+	Urticaria, rhinitis
13	7	M	Yes	No	0.52	13.5	ND	Rhinitis, vomiting
14	8	M	Yes	Yes	7.5	8	ND	Asthma, urticaria
15	7	M	Yes	Yes	0.86	6	+	Urticaria
16	5	F	No	No	0	8	+	Angioedema, abdominal pain
17	14	M	No	Yes	> 100	8	ND	Vomiting, diarrhoea
18	6	M	No	Yes	1.09	6	+	Urticaria, angioedema
19	7	F	Yes	No	0	9.5	+	Disphonia, diarrhoea
20	9	M	No	Yes	6.56	13	ND	Urticaria
21	6	M	Yes	No	2.21	15	ND	Angioedema
22	10	F	No	Yes	22.5	15	ND	Abdominal pain, vomiting
23	6	M	Yes	Yes	0.48	6.5	+	Cutaneous rash

*sIgE to egg white.

[†]Papule mean diameter with pasteurized egg white.

[‡]Oral challenge test.

AD, atopic dermatitis; SPT, skin prick test; sIgE, specific IgE; ND, not done.

who needed longer to achieve tolerance; the mean SPT to egg white in the latter group was 11.2 mm, which was 2.6 mm larger than in the former group ($P=0.037$); and mean sIgE levels to egg white and ovomucoid were 18.6 and 11.6 kU/L, respectively, in the group that achieved tolerance in more than 5 days, compared with 4.35 kU/L ($P=0.005$) and 2.15 kU/L ($P=0.009$), respectively, in patients who were desensitized in 5 days.

Eighteen (78.3%) of the 23 patients suffered at least one allergic reaction during desensitization; in total, there were 35 mild reactions and 20 moderate ones. There were no severe reactions. Three of the five patients who did not suffer any reaction during the desensitization procedure had a positive challenged test in the previous 3 months and one had an unequivocal reaction to egg a few weeks before. The other patient (patient no. 8) had an sIgE of 28.1 kU/L. Seven patients reacted to an omelette after they had tolerated 8 mL of raw egg white, but all of these

reactions were mild. The responses of each patient to desensitization are presented in Table 3.

The minimum quantity of egg white that produced a reaction was 0.005 mL (0.65 mg of powdered egg white) and the mean $\pm$ SD dose was 1.17 mL (155 mg) $\pm$ 2.01 mL.

To date, the length of follow-up of the patients has been between 6 and 14 months, with almost no incidents.

Despite usually tolerating egg ingestion, a 17-year-old girl (patient no. 9) reported contact urticaria with raw egg and occasional abdominal pain after the ingestion of cooked egg, coinciding with stress or menstruation. These symptoms disappeared after several months and the patient was completely asymptomatic at the 6-month visit. Patient no. 10 had an episode of sudden vomiting 1 h after eating an omelette and when he was asleep. He was seen in an emergency department and recovered within few minutes with corticosteroid therapy; no adrenaline was used. Unfortunately, no blood tests were taken

Table 3. Response to desensitization

Subject no	MRD	Symptoms	Number of reactions	Type of egg*	Days [†]
1	0.2	Oral pruritus, perioral erythema	2 mild	RE	5
2	2	Lip and eyes angioedema, rhinitis, cutaneous rash, vomiting	1 mild 3 moderate	RE	80
3	6	Perioral urticaria	1 mild	RE	5
4	6	Oral pruritus, abdominal pain	2 mild	RE	5
5	0.5	Pharyngeal tightness, lip angioedema, abdominal pain	1 mild 1 moderate	RE	7
6	0.05	Abdominal pain, vomiting, rhinoconjunctivitis, cutaneous rash	2 mild 4 moderate	RE	60
7	–	None	0	–	5
8	–	None	0	–	5
9	0.005	Pharyngeal pruritus, abdominal pain, dysphonia, rhinitis, vomiting	4 mild 3 moderate	RE	7
10	4	Nausea, abdominal pain	1 mild	RE	5
11	–	None	0	–	5
12	0.1	Oral pruritus, mild urticaria	2 mild	RE, O	5
13	0.05	Abdominal pain	2 mild	RE	5
14	0.1	Rhinitis, vomiting abdominal pain, urticaria	2 mild 2 moderate	RE, O	9
15	0.1	Oral pruritus, mild urticaria	2 mild	RE, O	5
16	–	None	0	–	5
17	0.5	Vomiting, diarrhoea, abdominal pain	3 mild 2 moderate	Abandoned at 0.5 mL	–
18	0.005	Oral pruritus, mild urticaria	3 mild	RE, O	5
19	0.2	Oral pruritus	1 mild	RE	5
20	0.2	Oral pruritus, abdominal pain, urticaria	1 mild 3 moderate	RE, O	6
21	0.2	Oral pruritus, rhinitis, vomiting, urticaria.	3 mild 1 moderate	RE, O	6
22	1	Oral pruritus, abdominal pain, urticaria	2 mild 1 moderate	RE, O	6
23	–	None	0	–	5

*Type of egg the patients reacted to: RE, raw egg; O, omelette.

[†]Days to complete desensitization.

MRD, minimum reacting dose (mL raw pasteurized egg white).

Table 4. SPT, sIgE and sIgG to egg white at follow-up

	Baseline	3 weeks	3 months	6 months
SPT [†] (mm)	9.09 (2.61)	ND	7.32 (4.12)	6.78 (3.47)*
sIgE [†] (kU/L)	9.87 (21.11)	9.25 (20.97)	3.36 (3.62)	3.6 (4.02)*
sIgG [†] (mg/L)	0.59 (0.8)	7.12 (9.82)*	6.32 (8.02)*	11.07 (11.38)*

* $P < 0.05$ compared with the baseline.

[†]Mean and SD.

SPT, skin prick test; sIgE, specific IgE; sIgG, specific IgG; ND, not done.

for serum tryptase measurement at that moment. He had tolerated daily cooked egg during the 3 previous months. Thirty-six hours later an oral challenge test was performed with cooked egg with good tolerance and since that time he has been eating egg and has had no further reactions.

One patient became symptomatic again on egg exposure owing to poor adherence. He had reduced and spaced out the amount of egg intake: at the 3-month visit, he had eaten less than a quarter of an egg in the previous week. He could not tolerate 1 mL of raw egg white on a new challenge test. This is the only patient who initially refused the regular egg intake; the other patients showed no problem regarding the introduction of egg into their diets.

Desensitization led to a fall in the mean values of the weal size and sIgE levels and an increase in sIgG levels, although the differences compared with baseline were only significant at 6 months for SPT and sIgE (Table 4). sIgG levels were significantly different from baseline at the 3-week follow-up.

Discussion

The aim of this study was to develop a practical rush desensitization protocol for patients allergic to egg in order to reduce the period of time at risk of reactions in the case of accidental ingestion of this food and to offer an alternative regimen adaptable to school time and other circumstances of the children.

All children over 5 years of age who fulfilled the inclusion criteria were included, without taking into account the severity of their allergy. This age was selected for two reasons: first, there is a reduction in the rate of acquisition of tolerance after this age, and second, this is the time when children acquire greater autonomy and may be exposed to a higher risk of accidental egg ingestion.

Pasteurized egg white was used for its ease of handling and safety against biological contamination; furthermore, there are no allergenic differences between this product and natural raw egg [30]. Egg is one of the foods whose allergenicity is most altered by cooking or processing. As demonstrated by Lemon-Mulé *et al.* [31], raw egg white is more allergenic than egg white prepared for consumption using common cooking methods (scrambled, boiled, etc.), and egg prepared in these ways is much more allergenic

than after baking at high temperatures with flour [32]. In fact, according to the study by Lemon-Mulé *et al.* [33] and as occurs with milk allergy, 74% of patients allergic to egg can tolerate this food in baked cakes. These facts are important when choosing the method of egg preparation for oral food challenges and for desensitization regimens. Despite these considerations, desensitization was started with raw rather than cooked egg white as this facilitated dilution and the accurate preparation of the very small doses required at the beginning of the protocol. There would be no need to achieve tolerance to a whole raw egg as it is not usually eaten uncooked in that amount and it is much more dangerous in egg-allergic patients. However, some raw egg white is frequently ingested in incompletely cooked eggs or even raw in other foods such as mayonnaise or ice cream (500 mL of mayonnaise or ice cream contains approximately one raw egg). We considered that tolerance to 8 mL of raw egg white (more than a quarter of the white of a whole egg) should be sufficient to protect patients from egg contained in a normal diet.

This regimen achieved desensitization in 86.9% of patients, similar to the results obtained with other slower egg desensitization regimens [8, 9], and better than those reported by some authors [13]. Most of the patients achieved tolerance to egg within 5 days, representing a substantial reduction in the time required compared with earlier protocols for this allergen [7, 9, 13], and a few days shorter than the only published rush regimen [23]. In that study published by Itoh *et al.*, all six patients included were successfully desensitized; they used raw (powdered) egg white and switched to cooked egg when a certain quantity was tolerated (1 g), as we did in our study. This, together with the fact that all the doses were given under medical supervision, in controlled circumstances rather than at home, could explain the good results in both studies, even though the subjects included in the Japanese study had severe egg allergy.

All the reactions in our study were mild or moderate, none was severe, and there were no reactions with the first dose of the proposed regimen, all of which would indicate a significant safety margin. In order for staff to be aware of any minimal symptom, patients did not receive prophylactic treatment with antihistamines; this could explain the numerous mild reactions observed. There were almost no incidents during follow-up and none of the patients suffered a recurrence of symptoms on ingestion of egg (except for the patient who did not comply with the regular intake of egg). The children tolerated not only one cooked egg but also other foods that contain raw egg, such as mayonnaise and ice cream.

For safety and ethical reasons, challenge tests with egg white were not performed in patients who showed sIgE or SPTs to raw egg highly suggestive of symptomatic allergy [25, 26]. This could be considered a limitation of our study, although most of these patients developed reactions

during the desensitization procedure, confirming the symptomatic allergy to egg. Only two of them did not react to egg during the protocol. These are the only cases in which there could be some doubt about the diagnosis of symptomatic egg allergy. However, even after removing those two patients from the analysis, the regimen offered a good rate of desensitization (85.7%).

The patient who abandoned the desensitization protocol had the highest sIgE level of the group, whereas the two patients who had to be switched to the slower protocol did not differ in this determination from the rest of the group. However, the 5-day regimen appears to be more successful in patients with smaller SPT reactions and lower levels of sIgE to egg proteins. More patients should be included to confirm that very high levels of sIgE would be a relative contraindication for this rush regimen.

Given the slow rate of change in the SPT and sIgE, becoming significantly different only after several months of tolerance, we believe that this is a consequence or an epiphenomenon and not the mechanism of desensitization. sIgG was already elevated at the first control, 3 weeks after desensitization. Earlier controls should have been performed to confirm that these changes parallel the clinical tolerance to egg.

Another limitation of our study was the lack of a control group, although, given the short period of desensitization, it would be practically impossible to acquire

tolerance naturally in that time and it would be difficult to justify the performance of a new challenge test in the control group only a week after a positive one. However, it would be interesting to evaluate the long-term immunological response to egg in both desensitized patients and a control group.

In conclusion, this study confirms that tolerance to egg can be achieved within a matter of days in symptomatic allergic patients, even in patients with episodes of anaphylaxis. The proposed protocol is relatively safe, although not risk free; the procedure must therefore be carried out in specialized centres with staff experienced in the treatment of this type of reaction and with sufficient means to perform close clinical monitoring of the patients.

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The authors declare that they have no conflicts of interest.

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