

Oral immunotherapy protocol for hen's egg allergic children: Improving safety

To the Editor,

Hen's egg (HE) allergy is one of the most common food allergies in childhood, affecting 1%-2% of young children. Usually, 66% are resolved 5 years after diagnosis.¹ The new EAACI guidelines in allergen immunotherapy (2017) propose that oral immunotherapy (OIT) with HE has a grade B recommendation, as a treatment option in children with persistent allergy, from around 4 to 5 years of age. As HE is a common ingredient in many foods, strict avoidance is difficult. Recent studies demonstrate that a large percentage of HE-allergic patients tolerate heated forms of egg. The median age to become tolerant of heated HE is 5.6 years while to raw egg is 10.3 years old.^{2,3} Moreover, tolerance to baked foods occurs at an earlier age.^{2,3} Once diagnosed, monitoring for allergy resolution requires immunological parameter follow-up, such as skin prick test (SPT), specific IgE (s-IgE) and an oral food challenge (OFC) when necessary. There are no reliable cut-off values that allow a firm diagnosis of raw, heated or baked HE allergy in order to avoid an OFC. According to the literature,⁴ raw egg allergy seems likely with an egg white (EW) s-IgE ≥ 7.3 KU/L in children older than 2 years and ≥ 1.7 KU/L in less than 2 years old. Oral immunotherapy (OIT) emerges as an experimental alternative for patients who have not achieved natural tolerance. OIT induces desensitization, defined as increasing the threshold dose while on therapy; however, the efficacy rates are very variable. Due to the heterogeneity of study protocols, complete desensitization can range from 55% to 100%.^{1,5,6} There are limited data on long-term tolerance without a daily maintenance dose, referred to as sustained unresponsiveness, which is not achieved by all patients undergoing OIT. However, a larger proportion of treated patients acquire tolerance in relation to those who follow a strict elimination diet.⁷ To date, there is a lack of immunological biomarkers that can be used as a prognostic predictor of success in OIT.

The lack of standardized protocols and patient's safety continue to be a source of concern. There are reports on early discontinuation due to adverse events in 12.5%-36% of children.^{1,8,9} Our group has previously published data regarding safety in a raw egg-OIT protocol, reporting adverse reactions in 7.6% of doses.¹ In order to improve safety, a new HE-OIT protocol was designed combining firstly, dilutions of raw EW, then hard-boiled EW and finally well-cooked omelet.

We recruited children over 5 years, with suggestive clinical history, SPT > 3 mm, EW s-IgE > 0.35 KU/L and a positive HE-OFC. OFC protocol started with 30 mg egg protein (hard-boiled

EW) up to a total dose of 7500 mg egg protein (well-cooked omelet). All patients underwent a 28-step HE-OIT protocol. The first 18 steps were given over 4 days in hospital: 10 increasing doses of diluted raw EW up to 8.3 mg of egg protein and the remaining 8 doses up to 150 mg of egg protein administered as hard-boiled EW. Diluted raw EW was chosen for the starting doses because we could not weight less than 10 mg of egg protein in hard-boiled EW. Afterwards, at day hospital, during 10 consecutive weeks, increasing amounts of hard-boiled EW up to 0.25 g of protein were reached, followed by an up-dose of well-cooked omelet. The final target was 7.5 g of egg protein (1 egg white and yolk in an omelette; Table 1). Maintenance dose was kept with one well-cooked omelet 3 times per week. Clinical and immunological data were collected. IgE-mediated symptoms at OFC and at the up-dosing phase were categorized as adverse events and registered; severity was classified using the proposed score by EAACI in the recently published position paper.¹⁰ Written informed consent was obtained. Quantitative variables are expressed in medians with interquartile range (IQR). Statistical analysis was performed with SPSS (IBM 2015). Results were considered statistically significant for $P < 0.05$.

Forty-three patients, 69.8% boys, were included. Median age at OFC was 9 years (7-12), 53.5% of patients had other food allergies, 46.5% atopic dermatitis, 42% asthma and 21% allergic rhinitis. Previous history of anaphylaxis to egg was reported by 48.8% of patients. Two patients did not undergo OFC due to anaphylaxis by accidental dietary egg exposure in the last 6 months. At OFC (n 41), six patients (14.6%) experienced local reactions (grade 1) and 35 patients had systemic reactions: 26 (63.4%) grade 2 and 9 patients (21.9%) more severe and potentially life-threatening reactions (grade 3). Median parameters at OFC were as follows: EW s-IgE 6.22 KU/L (1.87-24.85) OVM s-IgE 3.80 KU/L (1.75-14.90), EW SPT 10.42 mm (7.40-12.61) and OVM SPT 9.63 mm (7.32-11.72). Up-dosing phase was completed in 76.7% (33/43) of children. 23.3% (10/43) withdrew: seven patients because of adverse events, two teenagers who stopped taking the dose and one patient for family reasons (Figure 1). Adverse events occurred in 65.1% (28/43) of patients during the up-dosing phase: three patients (7.0%) had local reactions and 25 (58.1%) systemic reactions. Sixteen (37.2%) had grade two reactions and nine patients (20.9%) grade 3. Adrenaline was used in six children (6/9) with grade 3 reactions. Five were administered at day hospital to

TABLE 1 Hen's egg oral immunotherapy protocol

Day/Week	Egg	Dose	Egg protein
1st day			
1- to 2-h interval per doses	Raw EW	1/1000 1 mL	0.083 mg
	Raw EW	1/1000 2 mL	0.166 mg
	Raw EW	1/1000 3 mL	0.249 mg
	Raw EW	1/100 0.5 mL	0.415 mg
	Raw EW	1/100 0.7 mL	0.581 mg
	Raw EW	1/100 1 mL	0.83 mg
2nd day			
1- to 2-h interval per doses	Raw EW	1/100 2 mL	1.66 mg
	Raw EW	1/100 3 mL	2.49 mg
	Raw EW	1/100 5 mL	4.15 mg
	Raw EW	1/10 1 mL	8.3 mg
	Hard-boiled EW	0.1 g	10 mg
3rd day			
1- to 2-h interval per doses	Hard-boiled EW	0.1 g	10 mg
	Hard-boiled EW	0.2 g	20 mg
	Hard-boiled EW	0.3 g	30 mg
	Hard-boiled EW	0.5 g	50 mg
4th day			
1- to 2-h interval per doses	Hard-boiled EW	0.7 g	70 mg
	Hard-boiled EW	1 g	100 mg
	Hard-boiled EW	1.5 g	150 mg
2nd week	Hard-boiled EW	2.5 g	250 mg
3rd week	Omelet	3.75 g	468 mg
4th week	Omelet	5.6 g	700 mg
5th week	Omelet	7.5 g	937 mg
6th week	Omelet	11.2 g	1400 mg
7th week	Omelet	15 g	1800 mg
8th week	Omelet	20 g	2500 mg
9th week	Omelet	30 g	3750 mg
10th week	Omelet	45 g	5600 mg
11th week	Omelet	60 g	7500 mg

Abbreviation: EW, egg white.

patients with increasingly severe symptoms and a risk of a potentially life-threatening event. One patient needed adrenaline at home. Despite adrenaline injector having been recommended, only one family used it at home. Parents were afraid to use adrenaline and unable to grade the severity of the symptoms. All patients who required adrenaline more than twice withdrew the protocol during the up-dosing phase. From withdrawals, systemic reactions at initial OFC were registered in 80% of patients and in all of them during OIT (Tables 2 and 3). A total of 6044 doses were administered and adverse events occurred overall in 3% of doses. The rate of adverse events per dose was 7.3% in patients who withdrew and 1.4% in those who completed the up-dosing phase. No significant differences were found in total IgE, s-IgE or SPT

between withdrawals and patients who completed the up-dosing phase. However, having a systemic reaction during up-dosing phase increases the risk of withdrawals (OR 2.6, P 0.0024). Other predictors such as asthma, allergic rhinitis, atopic dermatitis and other food allergies were checked, and no dose-related reactions were identified.

Thirty-three patients are still in the maintenance phase, 22 completed 6 months. In this period, 3 (13.6%) patients had local reactions and 50% had systemic reactions (27.3% grade 2, 22.7% grade 3). Oral antihistamines were given to 30% of children, 20% required inhaled β_2 -agonistics, and no adrenaline was administered. S-IgE and SPT were evaluated in the maintenance phase at a mean time of 10.6 months (SD 2.76). Statistical significance

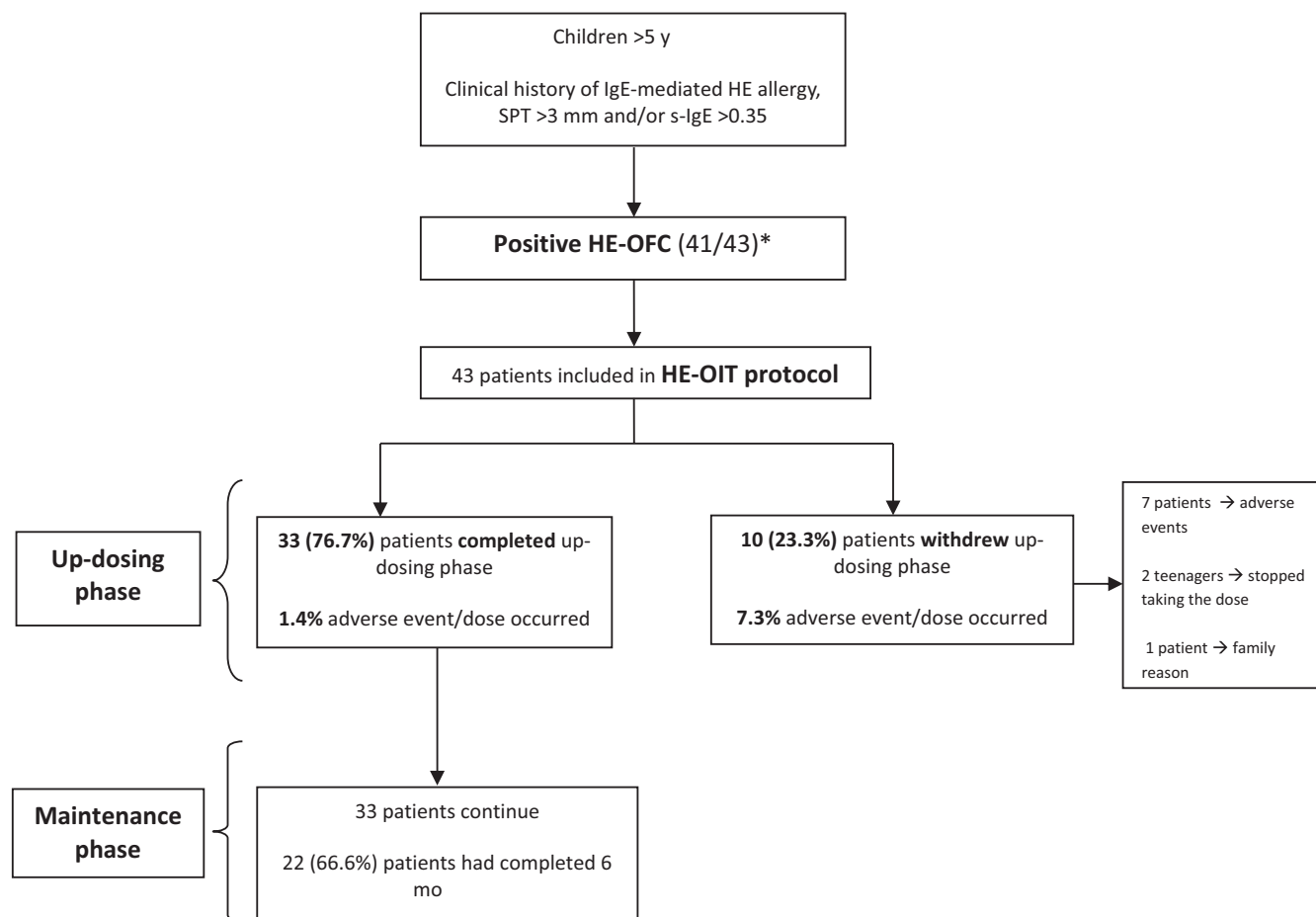


FIGURE 1 Study flow chart. HE-OFC, hen's egg oral food challenge; HE-OIT, hen's egg oral immunotherapy; s-IgE, specific IgE; SPT, skin prick test. *Two patients did not undergo HE-OFC because of recent severe reaction (<6 months)

	Completed up-dosing phase	Withdrawal up-dosing phase	Statistical significance
N patients (%)	33 (76.7)	10 (23.3)	
Rate of adverse events (%)	1.4	7.3	
Previous history anaphylaxis (n, %)	14 (42.4)	7 (70)	$P = 0.005$ OR 4.8
Systemic reaction at OFC (n, %)	28 (84.8)	8 (80)	$P = 0.656$
Systemic reaction at up-dosing phase (n, %)	15 (45.4)	10 (100)	$P 0.0024$ OR 2.6

Abbreviation: OFC, oral food challenge.

TABLE 2 Differences between patients who completed up-dosing phase and those who withdrew the protocol

between s-IgE and SPT at OFC and at the maintenance phase was obtained (Tables 2 and 3).

The proposed protocol has a low rate of adverse events overall during the up-dosing phase. Written reports confirm that this low rate is essential for treatment adherence and this was seen in our cohort as more than half (76.7%) of the patients completed this phase successfully. Adverse events per dose were markedly higher within withdrawals. In fact, having a previous history of anaphylaxis and/or a systemic reaction during up-dosing phase turned out to be a risk factor for

withdrawal with statistical significance. Our data report systemic reactions (grade 3) in 21.9% during OFC, 20.9% during up-dosing and 22.7% at the maintenance phase. Also, the adrenaline doses administered were directly related to drop-out. Despite the advice given to families on how to treat possible adverse events at home, prior to the start of the protocol, there is still fear or perhaps an underestimation by guardians and patients about their own symptoms and how and when to use the adrenaline auto-injector. In line with published data, no differences on s-IgE or SPT were observed between patients who

TABLE 3 Changes on immunological parameters at OFC time and after 6 mo of the maintenance phase of OIT (n 22)

	Start protocol	6 mo later	P value
EW s-IgE (KU/L) Median, IQR	2.93 (1.59-15.8)	2.15 (0.63-4.12)	<0.001
OVA s-IgE (KU/L) Median, IQR	2.2 (0.45-6.78)	0.64 (0.14-1.75)	<0.001
OVM s-IgE (KU/L) Median, IQR	3.11 (1.16-14.82)	1.56 (0.41-5.71)	<0.001
EW SPT (mm) Median, IQR	10.42 (7.89-12.81)	6.24 (3.39-9.48)	0.009
OVA SPT (mm) Median, IQR	7.54 (5.59-8.48)	4.61 (0-5.85)	0.005
OVM SPT (mm) Median, IQR	9.45 (7.67-10.76)	5.67 (4.85-8.97)	0.003

Abbreviation: IQR, interquartile range.

successfully completed the up-dosing phase and those who withdrew. Statistical differences were seen after 6 months in the maintenance phase on immunological parameters favouring an immune-modulatory effect which allows desensitization.

In conclusion, we consider ours a safe protocol due to a low rate of adverse events per doses and per patients. Discontinuation during up-dosing phase was associated with frequent symptoms and a higher rate of adverse event per doses. Suffering systemic reactions and the use of adrenaline had a negative effect that encouraged withdrawals. Immunological changes were obtained after 6 months of the maintenance phase. Nevertheless, a long-term follow-up is necessary to assess the true success of HE-OIT.

CONFLICT OF INTEREST

The authors have no conflict of interest in relation to this work.

AUTHOR CONTRIBUTION

All authors contributed to the study and the preparation of the following manuscript.

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