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ORIGINAL PAPER

Oral Specific Desensitization in Food-Allergic Children

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Abstract The possibility of obtaining oral desensitization in patients with food allergy is still a matter of debate. We decided to evaluate the safety and efficacy of standardized protocols for oral desensitization with the most common food allergens. Forty-two children (ages up to 16 years) diagnosed as affected by food allergy (on the basis of clinical history, skin prick tests, measurement of specific IgE, and double-blind, placebo-controlled food challenge) underwent a sublingual-oral desensitizing treatment according to new standardized protocols. The control group consisted of 10 patients who followed an elimination diet. The treatment was successfully completed by 85.7% of the patients. Specific IgE showed a significant decrease, while specific IgG_4 showed a significant increase, in all treated patients. The immunological modifications observed in our patients lead us to hypothesize that oral tolerance may be mediated by the same mechanisms as those involved in traditional desensitizing treatments for respiratory and insect sting allergy.

Keywords Food allergy · Oral desensitization · Milk allergy · Egg allergy · Fish allergy

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The first therapeutic approach to food-allergic patients is to eliminate the responsible food from the diet, but this is not always possible since it may be an essential component of the diet (such as milk or egg) or it may be difficult to avoid hidden allergens [1]. Moreover, the avoidance of foods such as milk or eggs can generate psychological or growth problems in children. In fact it has recently been demonstrated that children with milk allergy or multiple food allergies are at greater risk of growth problems or inadequate nutrient intake [2].

A chronic pharmacological approach with H_1-antihistamines, corticosteroids, or membrane stabilizers such as sodium cromolyn is not always successful in the prevention of allergic reactions.

Although some authors report that 87% of children affected by cow milk allergy/intolerance lose their hypersensitivity in the first 3 years of life [3], spontaneous desensitization may occur in 19–44% of patients following an elimination diet, but this process usually takes years [4–7]. So for all those children who do not lose their food hypersensitivity or cannot maintain an adequate diet regimen, desensitizing treatment should be taken into consideration [8]. Subcutaneous immunotherapy has been carried out, but with poor results and serious side effects [9–15].

Despite some negative reports [11, 13, 16–18], the possibility of inducing oral desensitization is still under discussion, since this approach has been successfully carried out by several authors [19–29]. Moreover, some authors have recently attempted oral desensitization in 21 children with cow milk allergy, obtaining interesting results [30].

In this paper we aim to evaluate the safety and efficacy of oral desensitization carried out according to new standardized protocols we have recently modified [29] in children (aged to 16 years) with food allergy.

Methods

Forty-two consecutive children (18 girls and 24 boys; ages 3 to 16 years) affected by food allergy were enrolled in the study and underwent a sublingual-oral desensitizing treatment. Fourteen of the 42 patients (7 males and 7 females; ages from 3 to 14 years) also suffered from atopic dermatitis. As the control group, we chose 10 patients (4 girls and 6 boys; ages 5 to 13 years) who just followed a strict elimination diet for 18 months. These patients were offered the desensitizing treatment but their parents refused because of work problems (they could not take their children to the control visits).

Diagnosis of food allergy was made based on the clinical history and an allergological workup: (a) skin prick tests, performed by using first standardized allergens and then fresh foods (prick-by-prick method: a wheal reaction <3 mm in diameter was considered negative (–); a reaction between 3 and 5 mm was ranked positive (+); between 5 and 10 mm, ++; and >10 mm, +++); (b) serum total and specific IgE level assessment (UniCAP; Pharmacia, Uppsala, Sweden); and (c) double-blind, placebo-controlled, food challenge (DBPCFC).

Double-blind placebo-controlled food challenge

The DBPCFC was carried out by administering the allergen diluted in vanillin (for milk, whole egg, albumen, apple, beans, and wheat) or by using opaque capsules (for cod). Preparation of the challenges was performed as follows: homogenate for apple; yolk and albumen administered separately for egg; and oral provocation test performed with dilutions of semolina (we boiled 1 g of semolina with 100 ml of water for 20 min, obtaining a solution containing 40 mg/ml semolina) and then with bread for wheat. Vanillin alone and opaque capsules were used as placebo.

The DBPCFC was carried out on 2 or 3 successive days by administering placebo or allergenic food, with a 3-day interval. In particular, we used the following successive doses, administered every 30 min.

- For milk: 0.001, 0.005, 0.01, 0.02, and 0.05 ml on day 1; 0.1, 0.2, 0.5, and 1 ml on day 2; and 4, 8, 16, 32, and 60 ml on day 3.
- For egg albumen: 0.001, 0.005, 0.01, 0.02, and 0.05 ml on day 1; 0.1, 0.2, 0.5, and 1 ml on day 2; and 2, 4, 8, and 16 ml on day 3;
- For egg yolk: 0.001, 0.005, 0.01, and 0.05 ml on day 1 and 0.1, 0.2, 0.5, 1, 2, and 4 ml and then the remainder on day 2;
- For cod: 1, 2, 3, and 4 mg on day 1; 10, 20, 30, and 40 mg on day 2; and 500 mg, then 1, 10, 40, and 100 g on day 3
- For wheat: 0.04, 0.2, 0.4, 0.8, 1.2, and 1.6 mg (of semolina) on day 1; 8, 20, 40, 80, and 200 mg, then 1 g (of semolina) on day 2; and 2, 5, 10, 20 and 30 g of bread on day 3.
- For apple: 10 and 100 mg, then 1, 2, 3, and 4 g on day 1; and 10, 20, 30, 40, and 50 g on day 2.

Patients were observed for 6 hr after the DBPCFC on an inpatient basis and a 7-day diary was kept by all patients to record the occurrence of any reaction. Provocation was stopped if adverse reactions were observed or the highest dose was reached. According to the current literature, DBPCFC was not performed in 15 patients with very high specific IgE levels or who had experienced life-threatening reactions [31].

Food challenges were scored as positive if one of the following combinations of clinical reactions and symptoms was observed:

- urticaria/angioedema or erythema with pruritus;
- rhinitis, rhinorrhea, or nasal obstruction;
- bronchial asthma;
- vomiting and/or diarrhea with abdominal pain;
- general malaise, collapse, or loss of consciousness.

Desensitization protocols

Next, on the basis of our previous experience [24, 29], a sublingual-oral desensitizing treatment was performed according to new standardized protocols adapted to paediatric patients (Tables 1–3). In particular, we administered food first diluted in water and then undiluted, at progressively increasing doses. The starting dilutions of the protocols were prepared by the nurses in our department and given to the patients. Then the patients' parents were told to prepare the remaining doses of the protocols themselves.

The first doses of the protocols were administered via the sublingual route and then swallowed after 2–3 min; when the highest doses were reached, the patients swallowed the food immediately. All patients underwent the desensitizing treatment at home and were followed in a day-hospital regimen every 15 days. Every patient was told to have at home an emergency kit: autoinjectable epineprine, betamethasone, and clorphenamine.

Regarding cod fish, we whisked for 3 min 25 g of boiled cod fish with 50 ml of water; then we added water to a final volume of 75 ml, obtaining a solution containing 0.33 mg/ml fish. For albumen we followed the same protocol used for whole egg.

Five of the 42 patients showed a positive clinical reaction to more than one food allergen; for this reason, they underwent one desensitizing protocol at a time for a total of 11 treatments. Finally, a total of 48 treatments were performed.

At the beginning of the protocol, sodium cromolyn (250 or 500 mg, according to the patient's age) or an

Table 1 Protocol for oral desensitization with cow's milk

Dilution: 1 drop of milk in 100 ml of water		Pure milk			
Days	Drops	Days	Dose	Days	Dose
From 1 to 3	1	From 37 to 39	1 drop	From 133 to 135	35 ml
From 4 to 6	3	From 40 to 42	2 drops	From 136 to 138	40 ml
From 7 to 9	6	From 43 to 45	3 drops	From 139 to 141	45 ml
From 10 to 12	10	From 46 to 48	4 drops	From 142 to 144	50 ml
From 13 to 15	15	From 49 to 51	5 drops	From 145 to 147	55 ml
From 16 to 18	20	From 52 to 54	6 drops	From 148 to 150	60 ml
		From 55 to 57	7 drops	From 151 to 153	65 ml
		From 58 to 60	8 drops	From 154 to 156	70 ml
		From 61 to 63	9 drops	From 157 to 159	75 ml
		From 64 to 66	11 drops	From 160 to 162	80 ml
		From 67 to 69	13 drops	From 163 to 165	90 ml
		From 70 to 72	16 drops	From 166 to 168	100 ml
		From 73 to 75	20 drops	From 169 to 171	110 ml
		From 76 to 78	24 drops	From 172 to 174	120 ml
		From 79 to 81	30 drops	From 175 to 177	130 ml
		From 82 to 84	36 drops		
		From 85 to 87	42 drops		
		From 88 to 90	48 drops		
		From 91 to 93	54 drops		
Dilution: 10 drops of milk in 100 ml		From 94 to 96	62 drops		
		From 97 to 99	70 drops		
		From 100 to 102	80 drops		
From 19 to 21	1	From 103 to 105	3 ml		
From 22 to 24	3	From 106 to 108	4 ml		
From 25 to 27	6	From 109 to 111	5 ml		
From 28 to 30	10	From 112 to 114	6 ml		
From 31 to 33	15	From 115 to 117	8 ml		
From 34 to 36	20	From 118 to 120	11 ml		
		From 121 to 123	15 ml		
		From 124 to 126	20 ml		
		From 127 to 129	25 ml		
		From 130 to 132	30 ml		
		Maintenance dose: 130 ml of milk (about 1 glass) at least two or three times a week			

Table 2 Protocol for oral desensitization with egg

Dilution: 1 drop of raw shaken egg (albumen + yolk) in 100 ml of water		Pure raw shaken egg	
Days	Drops	Days	Dose
From 1 to 3	1	From 61 to 63	1 drop
From 4 to 6	2	From 64 to 66	2 drops
From 7 to 9	3	From 67 to 69	3 drops
From 10 to 12	4	From 70 to 72	4 drops
From 13 to 15	5	From 73 to 75	6 drops
From 16 to 18	6	From 76 to 78	8 drops
From 19 to 21	8	From 79 to 81	10 drops
From 22 to 24	10	From 82 to 84	12 drops
		From 85 to 87	15 drops
		From 88 to 90	20 drops
		From 91 to 93	27 drops
Dilution: 10 drops of raw shaken egg (albumen + yolk) in 100 ml of water		From 94 to 96	37 drops
		From 97 to 100	50 drops
		From 101 to 104	2 ml
From 25 to 27	1	From 105 to 109	3 ml
From 28 to 30	2	From 110 to 113	4 ml
From 31 to 33	3	From 114 to 117	5 ml
From 34 to 36	4	From 118 to 121	6 ml
From 37 to 39	5	From 122 to 125	7 ml
From 40 to 42	6	From 126 to 129	8 ml
From 43 to 45	8	From 130 to 133	10 ml
From 46 to 48	11	From 134 to 137	12 ml
From 49 to 51	15	From 138 to 141	15 ml
From 52 to 54	20	From 142 to 145	20 ml
From 55 to 57	25	From 146 to 149	25 ml
From 58 to 60	30	From 150 to 153	30 ml[a]
		From 154 to 157	35 ml
		From 158 to 161	40 ml
		From 162 to 165	45 ml
		From 166 to 168	50 ml
Maintenance dose: 1 egg at least two or three times a week			

[a] As regards albumen allergy, we used the same doses and we shook the albumen only; desensitization was interrupted at that point since an albumen is about 30 ml.

H_1-antihsitamine (cetirizine or loratadine) was given 20 min before administration of the dose if any adverse reaction was observed. In these cases, when a reaction occurred, we asked the patients to reduce the dose by about 25% and then to increase the doses again.

After completing the desensitizing treatment, all patients were asked to eat the allergenic food at least twice a week to maintain the tolerance state. The maintenance dose was chosen on the basis of our previous experience (in fact, two adults who stopped eating the allergenic food lost their tolerance). At the end of the treatment, DBPCFC was performed in all patients, as already described.

Blood samples

Total and specific IgE and specific IgG_4 in the serum were detected with an immunoenzymatic assay (UniCAP [Pharmacia] was used to detect IgE and CAP FEIA [Pharmacia] was used to detect IgG_4) 6, 12, and 18 months after starting the protocol in all patients who completed the treatment successfully; skin prick tests were repeated 18 months later.

Pharmacia CAP FEIA and UniCAP are in vitro test systems based on ImmunoCAP technology for determination of circulating specific IgG_4 and IgE antibodies. The food allergens of interest, covalently coupled to ImmunoCAP, react with the specific IgE and IgG_4 in the patient's serum specimen. After washing away nonspecific IgE and IgG_4, enzyme-labeled antibodies against IgE and IgG_4 are added to form a complex. After incubation, unbound enzyme anti-IgE and anti IgG_4 are washed away and the bound complex is then incubated with a developing agent. After stopping the reaction, the fluorescence of the eluate is measured with a fluorocount. To classify test results, fluorescence for patient samples is compared directly with FU for standards run in parallel. The UniCAP System specific IgE measuring range is 0.35–100 kU_A/L; the CAP FEIA System specific IgG_4 measuring range is 0.15–30 mg/L.

Table 3 Oral specific desensitization

Cooked fish (boiled cod)	
Days	Daily dose
1 to 3	0.000033 mg
4 to 6	0.00033 mg
7 to 9	0.0033 mg
10 to 12	0.033 mg
13 to 15	0.33 mg
16 to 18	0.66 mg
19 to 21	1.32 mg
22 to 24	3.3 mg
25 to 27	6.6 mg
28 to 30	13.2 mg
31 to 33	33 mg
34 to 36	50 mg
37 to 39	66 mg
40 to 42	100 mg
43 to 45	132 mg
46 to 48	200 mg
49 to 51	264 mg
52 to 54	330 mg
55 to 57	429 mg
58 to 60	528 mg
61 to 63	660 mg
64 to 66	825 mg
67 to 69	1 g
70 to 72	1.5 g
73 to 75	2 g
76 to 78	3 g
79 to 81	4 g
82 to 84	5 g
85 to 87	6 g
88 to 90	7 g
91 to 93	8 g
94 to 96	9 g
97 to 99	12 g
100 to 102	14 g
103 to 105	16 g
106 to 108	18 g
109 to 111	20 g
112 to 114	23 g
115 to 117	27 g
118 to 120	32 g
121 to 123	37 g
124 to 126	42 g
127 to 129	47 g
130 to 132	52 g
133 to 135	57 g
136 to 138	62 g
139 to 141	67 g
142 to 144	72 g
145 to 147	78 g
148 to 150	85 g
151 to 153	92 g
154 to 156	100 g
Maintenance dose: 100 g of boiled cod at least twice a week	

Other tests

All patients with milk hypersensitivity underwent a lactose breath test to exclude the possibility of lactose intolerance. The patient with wheat hypersensitivity underwent some serological tests, such as measurement of IgA and IgG antigliadin and antiendomysial antibodies and anti-tTG (tissue transglutaminase) antibodies to exclude the possibility of celiac disease.

Statistical analysis

Shapiro-Francia test was used to evaluate normal distribution of raw data. Wilcoxon test for paired data was used to evaluate the differences in values of IgE and IgG_4 at different times. Statistical analyses were performed using the Stata 7.0 statistical software package. Statistical significance between treated- and control-group oral challenge results (after the desensitising treatment) was assessed by Fisher's exact test.

Results

Of the total number of 42 patients enrolled in our study, 13 were shown to be allergic to milk, 3 to milk and egg, 1 to milk and cod fish, 11 to egg, 2 to egg albumen, 1 to cod fish, egg albumen, and milk, 7 to cod fish, 1 to apple, 2 to wheat, and 1 to beans. In the control group, five patients were allergic to milk, four to egg, and one to fish.

Forty DBPCFC were carried out in 27 patients: the test was positive in 38 cases and negative in two. The two negative responses were obtained with egg yolk, and in these cases the patients underwent an oral desensitizing treatment with egg albumen only.

Mostly gastrointestinal (abdominal pain in 15 cases, nausea and/or vomiting in 9 cases) and cutaneous (urticaria/angioedema in 13 cases, erythema and/or pruritus in 14 cases) symptoms were presented by the patients; respiratory symptoms, such as rhinitis and bronchial asthma, were reported in 4 and 5 cases, respectively (for further details see Table 4).

The mean provoking doses were 19.92 ± 24.78 ml for milk, 4.04 ± 9.29 ml for egg albumen, 4.51 ± 5.42 ml for egg yolk, and 4.81 ± 5.68 g for cod fish.

The lactose breath test was negative in all patients with milk allergy. As regards the patient with wheat allergy, IgA and IgG antigliadin and antiendomysial antibodies and anti-tTG antibodies were negative.

Six of the 42 patients dropped out due to poor compliance. Finally, 36 patients underwent a sublingual-oral specific desensitization for a total of 42 treatments (in fact some patients were allergic to more than one food).

Table 4 Oral provocation test results

Patient	Sex, age	Food	Dose	Result of DBPCFC	Symptom(s)	Result of oral desensitization
1	M, 12	Whole egg	ND			Success
2	M, 11	Milk	60 ml	Positive	CH, AE	Success
3	F, 12	Egg yolk	1 ml	Positive	AP, N, IT	Success (with whole egg)
		Egg albumen	2.5 ml diluted 1:10	Positive	AP, C	
		Milk	60 ml	Positive	R, C	Success
4	M, 14	Beans	ND			Abandoned
5	M, 7	Cod fish	10 g	Positive	AP, AE	Success
6	M, 8	Egg yolk	6 ml	Positive	AP	Success (with whole egg)
		Egg albumen	1 ml diluted 1:100	Positive	IT, CH	
7	M, 11	Milk	ND			Success
8	F, 15	Egg yolk	6 ml	Positive	IT, E	Success (with whole egg)
		Egg albumen	1 ml	Positive	AP	
		Milk	3 ml	Positive	PH, N	Success
9	M, 4	Milk	2 ml	Positive	V, BA, U	Failure
10	F, 10	Egg albumen	30 ml	Positive	AP, U	Success
11	M, 5	Milk	0,1 ml	Positive	E, P	Success
12	F, 7	Wheat	0.64 mg	Positive	BA, R	Success
13	F, 4	Milk	ND			Abandoned
14	F, 4	Egg yolk	1.6 ml diluted 1:100	Positive	AE, P, E	Success (with whole egg)
		Egg albumen	0.7 ml diluted 1:10	Positive	E, AP, P	
		Milk	0.7 ml	Positive	E, P	Success
15	M, 7	Whole egg	ND			Success
16	F, 13	Milk	50 ml	Positive	BA, U	Success
17	M, 6	Milk	30 ml	Positive	V, AP, U	Success
18	F, 5	Milk	30 ml	Positive	U, AP, V	Success
		Cod fish	1.7 g	Positive	AP	Success
19	F, 4	Whole egg	ND			Failure
20	M, 13	Cod fish	ND			Success
21	M, 7	Egg albumen	5 ml	Positive	N, V, R, C	Partial tolerance (with whole egg)
		Egg yolk	10 ml	Negative		
22	F, 14	Apple	ND			Success
23	F, 5	Milk	1.75 ml	Positive	R, BA	Failure
24	F, 5	Whole egg	10 ml	Positive	AP, C	Success
25	M, 14	Cod fish	270 mg	Positive	U	Success
26	M, 12	Milk	ND			Success
27	F, 6	Milk	1 ml	Positive	BA, AE	Success
		Cod fish	15 g	Positive	V	Success
		Egg albumen	0.21 ml	Positive	V	Success
		Egg yolk	10 ml	Negative		
28	M, 7	Whole egg	ND			Success
29	F, 16	Egg albumen	0.1 ml diluted 1:100	Positive	IT, AE	Abandoned

Table 4 Continued.

Patient	Sex, age	Food	Dose	Result of DBPCFC	Symptom(s)	Result of oral desensitization
29	F, 16	Egg albumen	0.1 ml diluted 1:100	Positive	IT, AE	Abandoned
30	M, 6	Egg albumen	3.7 ml	Positive	AP, D	Abandoned (with whole egg)
		Egg yolk	14 ml	Positive	AP, D	
31	M, 11	Egg albumen	1.7 ml diluted 1:10	Positive	W, AE	Partial tolerance (with whole egg)
		Egg yolk	0.3 ml diluted 1:10	Positive	E	
32	F, 11	Milk	ND			Abandoned
33	M, 9	Cod fish	5 mg	Positive	AE, E	Success
34	F, 8	Milk	ND			Failure
35	M, 3	Milk	14 drops	Positive	P, W	Abandoned
36	F, 11	Whole egg	ND			Success
37	M, 15	Cod fish	5 g	Positive	P, E	Success
38	M, 4	Milk	ND			Success
39	M, 16	Cod fish	ND			Success
40	F, 7	Whole egg	ND			Success
41	M, 6	Cod fish	1.7 g	Positive	AP, D	Success
42	M, 6	Wheat	0.144 g	Positive	AE	Success

Note. AP, abdominal pain; N, nausea; IT, itching of the throat; C, conjunctivitis; R, rhinitis; AE, angioedema; PH, pharyngeal hyperemia; D, diarrhea; V, vomiting; BA, bronchial asthma; U, urticaria; E, erythema; P, pruritus; W, worsening of atopic dermatitis; CH, choking; ND, not done.

Desensitization was successful in 36 of the 42 treatments (85.7%; Table 5).

During the protocol in 11 of 36 cases (30.5%), the patients experienced some mild side effects, such as urticaria, vomiting, worsening of bronchial asthma or of atopic dermatitis, angioedema, and abdominal pain. When these side effects occurred patients were treated with oral H_1-antihistamines. Symptoms were then easily controlled by prophylactic administration before food ingestion of oral H_1-antihistamines in four cases and sodium cromolyn in seven cases for some days (generally from 15 to 30 days). In four patients (10%) treatment was stopped due to the occurrence of skin reactions (urticaria) or of gastrointestinal symptoms (diarrhea, vomiting, and abdominal pain) not controlled by administration of sodium cromolyn or H_1-antihistamines before food ingestion.

Stratifying patients on the basis of food allergy, the results can be summarized as follows (see Table 5).

- In patients with milk allergy (18 cases), the treatment was abandoned in 3 cases (because of poor compliance); 12 out of the remaining 15 patients completed successfully the desensitisation in 6 to 8 months till the dose of 130 ml; they then continued drinking milk and eating dairy products as much as they liked with no problems at all in about 1 month; in 3 patients treatment was stopped for the occurrence of uncontrolled side effects (vomiting, abdominal pain, bronchial asthma, worsening of atopic dermatitis);
- In patients with egg allergy (14 cases), the treatment was abandoned in 2 cases (because of poor compliance); 10 of the remaining 12 patients completed the desensitization successfully in 5–8 months; in 1 patient treatment was stopped due to the occurrence of uncontrolled side effects (urticaria). Another patient presented nausea and vomiting at the end of the treatment after eating a whole egg, but he could eat other foods containing egg, such as alimentary paste, ice creams, and cakes ("partial tolerance").
- Of the patients with albumen allergy (three cases), treatment was completed successfully in 5 months in two cases; the remaining case did not complete the desensitization due to the occurrence of uncontrolled side effects, but he could eat foods containing egg with no side effects (partial tolerance).
- In patients with cod fish allergy (nine cases), the treatment was completed successfully in 5–10 months in all cases.
- The two patients with wheat allergy completed the treatment successfully in 7 months.
- The patient with apple allergy completed the treatment successfully in 4 months.
- The patient affected by bean (one case) allergy did not complete the treatment (because of poor compliance).

Table 5 Results of oral desensitization

Food	Cases	Success	Partial tolerance	Failure	Lack of compliance
Milk	18	12	—	3	3
Whole egg	14	10	1	1	2
Egg albumen	3	2	1	—	—
Cod fish	9	9	—	—	—
Wheat	2	2	—	—	—
Apple	1	1	—	—	—
Bean	1	—	—	—	1
Total	48	36 (85.7%)	2 (4.8%)	4 (9.5%)	6

Skin prick tests, strongly positive at the beginning, turned completely negative or showed a marked decrease after 18 months in 27 of 36 patients (75%) who successfully completed the treatment, while the remaining 9 cases (25%) did not show any change. In particular, in 8 cases skin prick tests decreased from +++ to ++; in 9 cases, from +++ to +; in 5 cases, from ++ to +; and in 5 cases, from ++ to negative.

The DBPCFC was negative in all patients who successfully completed the desensitizing treatment.

Regarding patients with atopic dermatitis, 10 of 14 successfully completed the treatment, 1 dropped out because of poor compliance, and in 1 case we had to stop the treatment because of uncontrolled side effects. The remaining two patients (previously described) achieved just partial tolerance to whole egg and to egg albumen. Just 1 patient of 10 who completed the treatment showed clinical improvement of atopic dermatitis, while the other 9 continued to present periodic exacerbation of the disease.

During the oral desensitizing treatment, we observed a significant decrease in specific IgE after 6 ($P < 0.001$), 12 ($p = 0.004$), and 18 ($P = 0.002$) months and a significant increase in specific IgG_4 after 6 ($P < 0.001$), 12 ($P < 0.001$), and 18 ($P < 0.001$) months (Figs. 1 and 2).

Regarding the 10 patients in the control group, DBPCFC was still positive after 18 months of a strict elimination diet and no changes in skin prick tests or in vitro tests were observed. Moreover, the difference in DBPCFC results between treated patients and controls was statistically significant ($P < 0.001$).

The mean specific IgE value was 29.42 ± 39.23 kU_A/L for patients who completed the treatment successfully, while it was of 58.97 ± 29.34 kU_A/L for patients who failed the treatment (for patients allergic to milk and egg, specific IgEs to casein and to egg albumen were chosen, respectively). The difference between these two groups was not statistically significant.

The mean provoking dose for milk-allergic patients was 23.85 ± 25.87 ml for those who completed the treatment successfully and 9.58 ± 13.35 ml for those who failed treatment. The difference between the two groups was not statistically significant.

Discussion

At present, the treatment of food allergy is an unresolved problem. Subcutaneous desensitization for peanut allergy has been performed in some studies [14, 15], with a decrease in skin prick test reactivity and symptom score at the end of treatment. However, patients experienced severe side effects (some patients needed epinephrine) and no immunological modifications were observed.

Elimination diets may lead to malnutrition and/or eating disorders, especially if they include a large number of foods and/or are used for a long time. Moreover, the elimination of a single food may be very difficult. For example, milk can be found as a hidden allergen in several dairy products [1]. "High-risk" situations, such as eating at restaurants or friends' homes, should be avoided. Airborne food particles may induce allergic reactions in highly sensitive patients.

In our opinion, for these reasons, the possibility of oral desensitizing treatment should be considered. In the literature, the possibility of obtaining oral desensitization in patients with food allergy has always been considered with interest [29, 30], albeit with some skepticism [32].

In this paper we have described standardized protocols for oral desensitization in children affected by food allergy and followed in a day-hospital regimen. According to these protocols, the treatment was successful in 85.7% of patients completing the protocol. Prophylactic oral administration of sodium cromolyn or of an H_1-antihistamine (such as cetirizine or loratadine) was successfully performed in 11 patients presenting with mild side effects, without any need for epinephrine administration or hospitalization. So, even though some mild side effects occurred, the treatment should be considered safe and suitable for all children suffering from food allergy. Parents should be very thoroughly informed about the execution of the treatment since they follow their own children at home during the desensitizing protocol.

The occurrence of spontaneous desensitization in our patients can be considered unlikely, since this phenomenon generally takes years [3–7] and is related to strict avoidance of the offending food. Moreover, this observation is confirmed by the persistence of DBPCFC positivity in all patients in the control group. In our series, all patients were

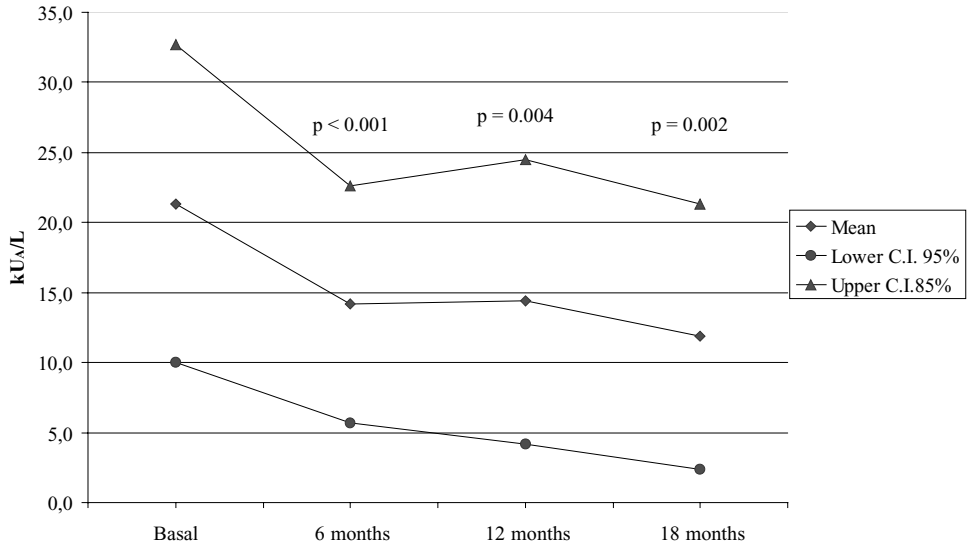

Fig. 1 Modifications of specific IgE values in patients who successfully completed the treatment

desensitized in a shorter time (approximately 3–10 months), eating food they were allergic to every day at increasing doses. On the basis of our experience, we think that all children who do not lose their hypersensitivity in the first 3–4 years of life should undergo desensitizing treatment. Moreover, it should be emphasized that two patients who did not complete the desensitizing protocol could eat foods containing egg, so we can think they achieved a partial tolerance to food allergens. This is very important since the presence of hidden allergens in other foods may lead to life-threatening reactions.

The great majority (9 of 10) of patients suffering from atopic dermatitis who completed the treatment did not show an improvement of the disease. This leads us to believe that in our patients food allergens were not involved in the pathogenesis of atopic dermatitis.

The exact mechanisms of the induction of oral tolerance are still debated, even though some hypotheses can be drawn: (a) antigen-driven suppression; (b) clonal anergy; (c) clonal deletion; (d) bystander suppression [33, 34]; and (e) shift from a Th2 to a Th1 response [26].

Recently, the World Health Organization stated that sublingual-swallow desensitizing immunotherapy has shown evidence of clinical efficacy in the treatment of respiratory allergies [36]. In particular, it has been demonstrated that in atopic patients the allergen can cross the gastrointestinal mucosa, leading to desensitization of the immune system. Analyzing our data, it can be hypothesized that sublingual-oral desensitization with food allergens could be mediated by a similar mechanism. In fact, in our series we observed in all cases a significant decrease in specific IgE and a significant increase in specific IgG_4 levels. In one patient [26]

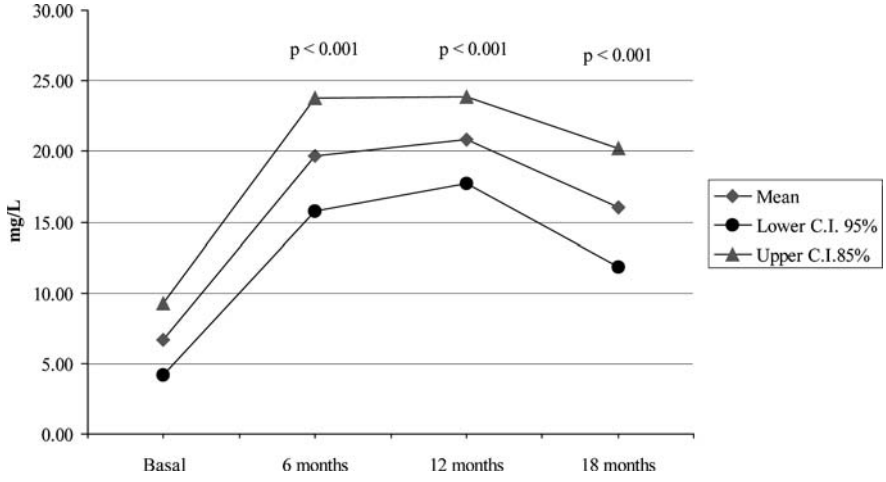

Fig. 2 Modifications of specific IgG_4 values in patients who successfully completed the treatment

we also found a decrease in IL-4 production (able to induce specific IgE synthesis) and an increase in IFN-γ production (able to inhibit specific IgE synthesis) by T lymphocytes, both spontaneously and after induction by allergen or mitogen; this led us to think that a switch from a Th2 to a Th1 response occurred. This pattern has been confirmed by the results of other work by our group regarding desensitization in 4 milk-allergic children [36] and in 59 patients (including adults and children) allergic to several different foods [29] and represents the typical immunological changes that have been observed in patients who underwent respiratory or insect sting allergy desensitization.

We also tried to explain the cause of the failure of treatment in four of our patients, but neither the mean IgE value nor the mean provoking dose were significantly different compared with the group that successfully completed the treatment. Even though the result was not statistically significant, we did observe that patients who failed the treatment had higher mean specific IgE values and lower provoking doses. These results should be confirmed in a larger group of patients.

Moreover, regarding a possible relationship between symptoms provoked by DBPCFC and the result of desensitizing treatment, we would like to emphasize that all three patients with milk allergy who failed the treatment presented bronchial asthma during the test. Just 3 patients of 19 who completed the treatment presented bronchial asthma (Table 4). Even though we studied only a few patients, the onset of bronchial asthma during DBPCFC seems to have an unfavorable effect on the result of oral desensitizing treatment.

So, although further studies (such as a randomized trial) are needed to reinforce the conclusions of this paper, oral desensitization may represent an alternative and safe approach in children with food allergy, in whom strict avoidance of specific allergens may cause nutritional, growth, and psychological problems [2].

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