

Oral desensitizing treatment in food allergy: clinical and immunological results

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Accepted for publication 30 November 2002

SUMMARY

Background: The possibility of inducing oral desensitization in patients with food allergy is still controversial and no standardized programmes are yet available.

Aim: To evaluate the safety and efficacy of oral desensitization in patients with allergy induced by the most common food allergens.

Methods: Fifty-nine patients with food allergy underwent an oral desensitizing treatment according to standardized protocols. The control group consisted of age- and sex-matched subjects, who followed a strict elimination diet. Specific immunoglobulin E and immunoglobulin G₄ were assessed at baseline and after 6, 12 and 18 months.

Results: The majority of patients (83.3%) successfully completed the treatment. During treatment, 51.1% of subjects experienced some mild side-effects, easily controlled by the oral administration of antihistamines or sodium cromolyn. Specific immunoglobulin E showed a significant decrease, whilst specific immunoglobulin G₄ showed a significant increase in all patients.

Conclusions: The immunological findings induced by oral desensitization in food allergy allow us to hypothesize that oral tolerance may be mediated by the same mechanisms as those involved in traditional desensitizing treatments for respiratory allergies. Moreover, the proposed standardized oral desensitization protocols may represent an effective alternative approach in the management of food-allergic patients.

INTRODUCTION

The search for a 'gold standard' treatment for food allergy continues to be an important matter of debate in the management of patients with allergic disease.

The elimination of the allergenic food represents the mainstay of treatment in preventing further reactions in sensitized patients, even when strict avoidance of the specific offending food is often an unrealistic therapeutic approach, as it may represent an essential component of the diet (such as eggs or milk), or it may be difficult to identify hidden or cross-reacting allergens.¹

When this option is unsuitable or when the clinical manifestations persist after this step has been taken, the use of pharmacological agents able to modify the inflammatory response is mandatory. Thus, H₁-antihistamines, corticosteroids and membrane stabilizers, such as sodium cromolyn, represent the benchmarks in the treatment of these patients, even when a chronic pharmacological approach is not always able to prevent the occurrence of clinical symptoms.

A spontaneous desensitization may occur in 19–44% of patients following an elimination diet, but this process usually takes years.^{2–6} Some authors have reported that 87% of children affected by cow milk allergy/intolerance lose their hypersensitivity in the first 3 years of life.⁷

For these reasons, in patients who cannot avoid food exposure in the environment (for example, cooks or

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milk workers), or who are unable to maintain an adequate diet regimen, a desensitization strategy should be considered.⁸ However, immunotherapy, based on an escalating dosage of subcutaneously administered purified allergen, has demonstrated limited efficacy and carries an important risk of anaphylaxis.^{9–15}

Despite some negative reports,^{11, 13, 16–18} the possibility of inducing oral desensitization is still under discussion, as this approach has been successfully carried out by several authors.^{19–30}

In this paper, we aimed to evaluate the safety and efficacy of oral desensitization carried out according to standardized protocols in patients with allergy induced by the most common food allergens.

METHODS AND MATERIALS

We enrolled 59 patients with food allergy (25 males and 34 females, aged between 3 and 55 years) referred to the Allergology Department. Of these, 32 were children aged less than 16 years.

As a control group, we chose 16 patients, aged 5–29 years, who refused to undergo oral desensitization. These patients had been following a strict elimination diet for 18 months.

The study was undertaken with the approval of the Catholic University Ethics Committee, and written informed consent was obtained from each patient or next of kin.

The diagnosis of food allergy was made through the clinical history and an allergological work-up: (i) skin prick tests, performed using standardized allergens initially and then fresh foods (prick-by-prick method: a wheal reaction of less than 3 mm in diameter was considered to be negative, between 3 and 5 mm was ranked +, between 5 and 10 mm was ranked ++ and, if larger than 10 mm, was ranked +++); (ii) assessment of serum total and specific immunoglobulin E (IgE) levels (UniCAP, Pharmacia, Uppsala, Sweden): the radioallergosorbent test was considered to be positive in the case of a specific IgE concentration of more than 0.70 kU_A/L; (iii) double-blind, placebo-controlled, food challenge.

The double-blind, placebo-controlled, food challenge was carried out by administration of the allergen diluted in vanillin (for milk, whole egg, albumin, apple, peach, lettuce, orange, beans and corn) or in opaque capsules (for cod and peanuts). Preparation of the challenges was performed as follows: homogenate for peach, apple,

corn, beans and lettuce; yolk and albumin administered separately for egg; orange juice for orange. Vanillin alone and opaque capsules were used as placebo.

The double-blind, placebo-controlled, food challenge was carried out on two different days (for the administration of placebo or allergenic food) with a 3-day interval. In particular, successive doses (for milk, albumin, yolk, apple, peach, lettuce, beans, corn and orange: 0.01, 0.1, 0.5, 1, 5, 10 and 30 mL; for cod: 0.001, 0.01, 0.02, 0.05, 0.5, 1, 2, 5, 10 and 20 g; for peanuts: 0.005, 0.05, 0.5, 5, 10 and 20 g), increasing every 30 min, were used. Patients were observed for 8 h after the double-blind, placebo-controlled, food challenge on an in-patient 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.

The food challenges were scored as positive if one of the following combinations of clinical reactions and symptoms was observed: (i) urticaria/angio-oedema or erythema with pruritus; (ii) rhinitis, rhinorrhoea or nasal obstruction; (iii) bronchial asthma; (iv) vomiting and/or diarrhoea with abdominal pain; or (v) general malaise, collapse or loss of consciousness.

All patients with milk hypersensitivity underwent a lactose breath test to exclude the possibility of lactose intolerance.

Oral desensitizing treatment was then performed according to standardized protocols,²⁶ as recently modified by our group (Tables 1–3). In particular, we administered food initially diluted in water, and then undiluted in progressively increasing doses. For fish, we whisked 25 g of boiled cod for 3 min with 50 mL of water; we then added water to a final volume of 75 mL to obtain a solution containing 0.33 mg/mL of fish. For albumin, we followed the same protocol as used for whole egg.

Six of the 59 patients showed a positive clinical reaction to more than one food allergen; for this reason, they underwent the desensitizing protocol for a total of 13 treatments. Sixty-six treatments were performed in total.

During the protocol, sodium cromolyn (250 or 500 mg, according to the patient's age) was given 20 min before food ingestion if clinical symptoms, such as pruritus or erythema, were observed. After completion of the desensitization treatment, all patients were asked to eat the allergenic food, at least twice a week, in order to maintain the tolerance state. At the end of

Table 1. Protocol for oral desensitization with cow's milk (modified from Patriarca *et al.*²⁶)

Days	Daily dose	Days	Daily dose
Starting dilution: 10 drops of milk in 100 mL of water		Pure milk	
1–3	1 drop	65–68	40 drops × 4
4–6	4 drops	69–72	50 drops × 4
7–9	6 drops	73–76	60 drops × 4
10–12	10 drops	77–80	4.5 mL × 3
13–15	12 drops	81–84	6 mL × 3
16–18	18 drops	85–88	6 mL × 4
Pure milk		89–92	7 mL × 4
19–21	1 drop	93–96	12 mL × 4
22–24	2 drops	97–100	15 mL × 4
25–27	3 drops	101–104	15 mL × 5
28–30	4 drops	105–108	20 mL × 3
31–33	6 drops	109–112	30 mL × 3
34–36	8 drops	113–116	40 mL × 3
37–40	10 drops	117–120	50 mL × 2
41–44	16 drops	121–124	65 mL × 2
45–48	24 drops	125–128	80 mL × 2
49–52	32 drops	129–132	100 mL
53–56	40 drops	133–136	120 mL
57–60	40 drops × 2	Maintenance dose: 120 mL of milk (about 1 glass) at least 2–3 times a week	
61–64	40 drops × 3		

treatment, the double-blind, placebo-controlled food challenge was not repeated, as patients were then able to eat a large amount of the allergenic food without any side-effects.

Total and specific IgE and specific IgG₄ in the serum were detected with an immuno-enzymatic assay [UniCAP (Pharmacia, Uppsala, Sweden) was used to detect IgE and CAP FEIA (Pharmacia) was used to detect IgG₄] at 6, 12 and 18 months after starting the protocol in all patients who successfully completed the treatment; skin prick tests were repeated 18 months later.

The Pharmacia assays CAP FEIA and UniCAP are *in vitro* test systems based on ImmunoCAP technology for the determination of circulating specific IgG₄ and IgE antibodies. The food allergens of interest, covalently coupled to ImmunoCAP, react with the specific IgE and IgG₄ in the patient's serum specimen. After washing away non-specific IgE and IgG₄, enzyme-labelled antibodies against IgE and IgG₄ are added to form a complex. After incubation, unbound enzymes anti-IgE and anti-IgG₄ are washed away and the bound complex is then incubated with a developing agent. After stopping the reaction, the fluorescence of

Table 2. Protocol for oral desensitization with egg (modified from Patriarca *et al.*²⁶)

Days	Daily dose	Days	Daily dose
Starting dilution: 10 drops of shaken egg (albumin and yolk) in 100 mL of water		Pure shaken egg	
1–3	1 drop	61–63	15 drops × 3
4–6	2 drop	64–66	20 drops × 3
7–9	4 drops	67–69	25 drops × 3
10–12	4 drops × 2	70–72	35 drops × 3
13–15	4 drops × 3	73–75	50 drops × 3
16–18	6 drops × 3	76–79	3 mL × 3
19–21	8 drops × 3	80–83	4 mL × 3
22–24	12 drops × 3	84–87	5 mL × 3
25–27	16 drops × 3	88–91	5 mL × 4
28–30	26 drops × 3	92–95	7 mL × 3
31–33	36 drops × 3	96–99	7 mL × 4
Pure shaken egg		100–103	10 mL × 3
34–36	1 drop	104–107	10 mL × 4
37–39	2 drops	108–111	15 mL × 3
40–42	3 drops	112–115	20 mL × 3
43–45	4 drops	116–119	25 mL × 2
46–48	6 drops	120–123	30 mL × 2*
49–51	8 drops	124–127	35 mL × 2
52–54	10 drops	128–131	40 mL × 2
55–57	10 drops × 2	132–135	45 mL
58–60	10 drops × 3	136–139	50 mL (1 egg)
Maintenance dose: 1 egg at least 2–3 times a week			

* For albumin allergy, we used the same doses and shook the albumin only; desensitization was interrupted at this point as the volume of albumin is about 30 mL.

the eluate is measured with a fluorocounter. To classify the test results, the fluorescence of the patient's sample is compared directly with the fluorescence of standards run in parallel. The UniCAP specific IgE measuring range is: 0.35–100 kU_A/L; cut-off value, ≥0.70 kU_A/L; <0.70 kU_A/L shows a negative test result. The CAP FEIA specific IgG₄ measuring range is: 0.15–30 mg/L.

Statistical analysis was performed by STATA 6.0 TM (College Station, TX, USA). The normal distribution of continuous variables was evaluated using the Shapiro–Francis test. When the distribution was normal, Student's *t*-test was used (IgE values at baseline, 6 and 12 months and IgG₄ values at baseline). Non-normal variables (IgE values at 18 months and IgG₄ values at 6, 12 and 18 months) were evaluated by a non-parametric test (Wilcoxon–Mann–Whitney test). A *P* value of <0.05 was considered to be statistically significant. All values

Table 3. Protocol for oral desensitization with fish (modified from Patriarca *et al.*²⁶)

Days	Daily dose	Days	Daily dose
Cooked fish (boiled cod)		Cooked fish (boiled cod)	
1–3	0.000033 mg	85–87	6 g
4–6	0.00033 mg	88–90	7 g
7–9	0.0033 mg	91–93	8 g
10–12	0.033 mg	94–96	9 g
13–15	0.33 mg	97–99	12 g
16–18	0.66 mg	100–102	14 g
19–21	1.32 mg	103–105	16 g
22–24	3.3 mg	106–108	18 g
25–27	6.6 mg	109–111	20 g
28–30	13.2 mg	112–114	23 g
31–33	33 mg	115–117	27 g
34–36	50 mg	118–120	32 g
37–39	66 mg	121–123	37 g
40–42	100 mg	124–126	42 g
43–45	132 mg	127–129	47 g
46–48	200 mg	130–132	52 g
49–51	264 mg	133–135	57 g
52–54	330 mg	136–138	62 g
55–57	429 mg	139–141	67 g
58–60	528 mg	142–144	72 g
61–63	660 mg	145–147	78 g
64–66	825 mg	148–150	85 g
67–69	1 g	151–153	92 g
70–72	1.5 g	154–156	100 g
73–75	2 g	157–159	120 g
76–78	3 g	160–162	140 g
79–81	4 g	163–165	160 g
82–84	5 g	Maintenance dose: 160 mg of boiled cod at least twice a week	

were two-tailed. Statistical significance between treated and control groups was assessed by Fisher's exact test.

RESULTS

Of the total number of 59 patients enrolled in our study, 29 were allergic to milk, 15 to whole egg, three to albumin, 11 to fish, two to orange and six to one of the following allergens: peanut, corn, peach, apple, lettuce and beans. Six patients were allergic to more than one food allergen (one patient allergic to egg, fish and milk, three to egg and milk, one to orange and lettuce and one to milk and fish). Moreover, 12 of the 59 patients dropped out due to poor compliance (they interrupted treatment because of job or, if children, school

problems). Overall, 47 patients underwent oral desensitization with a total of 54 treatments.

The lactose breath test was negative in all patients with milk allergy.

Desensitization was successful in 45 of the 54 treatments (83.3%). During the protocol, 51.1% of patients experienced side-effects, such as urticaria, angio-oedema or abdominal pain. In all cases, symptoms were easily controlled by the administration of H₁-antihistamines or sodium cromolyn.

In nine patients (16.7%), treatment was stopped due to the occurrence of skin reactions (urticaria) or gastrointestinal symptoms (diarrhoea, vomiting and abdominal pain) not controlled by oral administration of sodium cromolyn or H₁-antihistamines.

By stratifying patients on the basis of food allergy, the results can be summarized as follows:

- in patients with milk allergy (29 patients), the treatment was interrupted in five cases; 19 of the remaining 24 patients (79.2%) completed the desensitization in 3–12 months; in five patients, treatment was stopped due to the occurrence of uncontrolled side-effects;
- in patients with egg allergy (15 patients), the treatment was interrupted in two cases; 11 of the remaining 13 patients (84.6%) completed the desensitization in 3–8 months; in two patients, treatment was stopped due to the occurrence of uncontrolled side-effects;
- in patients with albumin allergy (three patients), the treatment was completed in 3–5 months in two cases; the remaining one patient did not complete the desensitization due to the occurrence of uncontrolled side-effects;
- in patients with fish allergy (11 patients), the treatment was interrupted in two cases; eight of the remaining nine patients (88.9%) completed the desensitization in 4–10 months; the remaining one patient did not complete the desensitization due to the occurrence of uncontrolled side-effects;
- in patients with orange (two patients), apple (one patient) and peach (one patient) allergy, the treatment was completed in 3 months;
- in patients with corn allergy (one patient), the treatment was completed in 8 months;
- all patients affected by bean (one patient), lettuce (one patient) and peanut (one patient) allergy did not complete the treatment.

Table 4. Results of oral desensitization

Food	Cases	Results
Milk	29	Interruptions: 5 Positive: 19 Withdrawn: 5
Whole egg	15	Interruptions: 2 Positive: 11 Withdrawn: 2
Albumin	3	Positive: 2 Negative: 1
Fish	11	Interruptions: 2 Positive: 8 Withdrawn: 1
Orange	2	Positive: 2
Apple	1	Positive: 1
Corn	1	Positive: 1
Beans	1	Interruptions: 1
Peanut	1	Interruptions: 1
Lettuce	1	Interruptions: 1
Peach	1	Positive: 1
Total	66	Interruptions: 12 Positive: 45 (83.3%) Withdrawn: 9 (16.7%)

Table 5. Results of oral desensitization in children (aged less than 16 years)

Food	Cases	Results
Milk	16	Interruptions: 3 Positive: 10 Withdrawn: 3
Egg	9	Positive: 8 Withdrawn: 1
Albumin	3	Positive: 2 Withdrawn: 1
Fish	7	Positive: 7
Apple	1	Positive: 1
Bean	1	Interruptions: 1
Total	37	Interruptions: 4 Positive: 28 (84.8%) Withdrawn: 5 (15.12%)

We did not find any difference between adults and children (Tables 4–6).

Skin prick tests, strongly positive at the beginning, were completely negative or showed a marked decrease after 18 months in 35 of 45 patients (77.8%) who successfully completed the treatment; in the remaining 10 cases (22.2%), there was no change. In particular, in 15 cases the skin prick tests decreased from +++ to ++, in 10 cases from +++ to +, in five cases from ++ to + and in five cases from ++ to negative.

Table 6. Results of oral desensitization in adults

Food	Cases	Results
Milk	13	Interruptions: 2 Positive: 9 Withdrawn: 2
Whole egg	6	Interruptions: 2 Positive: 3 Withdrawn: 1
Fish	4	Interruptions: 2 Positive: 1 Withdrawn: 1
Orange	2	Positive: 2
Corn	1	Positive: 1
Peanut	1	Interruptions: 1
Lettuce	1	Interruptions: 1
Peach	1	Positive: 1
Total	29	Interruptions: 8 Positive: 17 (81%) Withdrawn: 4 (19%)

During the oral desensitizing treatment, we observed a significant decrease in specific IgE after 6 ($P < 0.01$), 12 ($P < 0.01$) and 18 months ($P < 0.01$), and a significant increase in specific IgG₄ after 6 ($P < 0.01$), 12 ($P < 0.01$) and 18 months ($P < 0.01$) (Figure 1).

For the 16 patients in the control group, double-blind, placebo-controlled, food challenge 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 between treated patients and controls was statistically significant ($P < 0.001$).

DISCUSSION

At present, the management strategies for food allergy are still controversial.

Subcutaneous desensitization for peanut allergy has been performed by some authors, with a decrease in skin prick test reactivity and symptom score at the end of treatment.^{14, 15} However, patients experienced severe side-effects [some patients needed adrenaline (epinephrine)] and no immunological modifications were observed.

The possibility of obtaining oral desensitization in patients with food allergy has always been considered with interest, albeit with some scepticism.³¹

In this paper, we have described standardized protocols for oral desensitization in patients affected by food allergy, followed in a day-hospital regimen. Treatment was successful in 83.3% of patients completing the

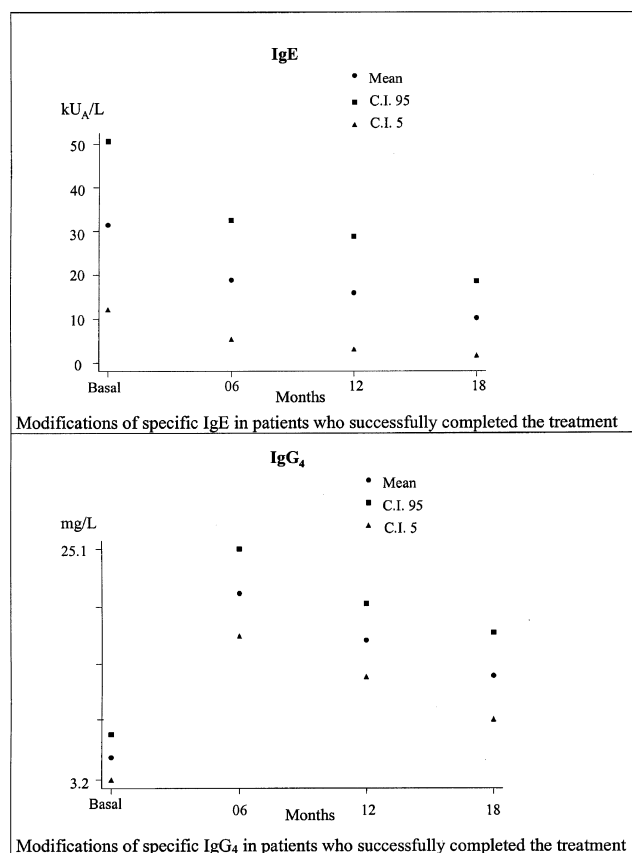


Figure 1. Modifications of specific immunoglobulin E (IgE) and immunoglobulin G₄ (IgG₄) during oral desensitization. C.I., confidence interval.

protocols. Prophylactic oral administration of sodium cromolyn or cetirizine was successfully performed in patients presenting with mild side-effects, without any need for adrenaline (epinephrine) administration or hospitalization.

The occurrence of spontaneous desensitization in our patients can be ruled out, as this phenomenon generally takes years,²⁻⁶ and is related to strict avoidance of the offending food. Moreover, this observation is confirmed by the persistence of double-blind, placebo-controlled, food challenge positivity in all patients in the control group. In our series, all patients were desensitized in a short time (approximately 4–8 months), eating every day, at increasing doses, the offending food.

The exact mechanisms of induction of oral tolerance are still under debate, but some hypotheses can be proposed: (i) antigen-driven suppression; (ii) clonal anergy; (iii) clonal deletion; and (iv) bystander suppression.^{32, 33}

Recently, the World Health Organization has reported that sublingual-swallow therapy shows evidence of clinical efficacy in the treatment of respiratory allergies.³⁴ In particular, it has been demonstrated that, in atopic patients, the allergen can cross the gastrointestinal mucosa, leading to a desensitization of the immune system. By analysing our data, it can be hypothesized that oral desensitization with food allergens could be mediated by a similar mechanism. Indeed, in our series, we observed a significant decrease in specific IgE and a significant increase in specific IgG₄ levels in all cases. In one patient, we also found a decrease in interleukin-4 (able to induce specific IgE synthesis) and an increase in interferon- γ (able to inhibit specific IgE synthesis) production by T lymphocytes, both spontaneously and after induction by allergen or mitogen.²⁸ This pattern has been confirmed by the results of other work by our group with regard to desensitization in four milk-allergic children,³⁵ and represents the typical immunological changes that have been observed in patients who have undergone respiratory allergy desensitization.

Therefore, although further studies are needed to reinforce the conclusions of this paper, the proposed protocol for oral desensitization may represent an alternative approach in patients with food allergy, especially children, in whom strict avoidance of specific allergens is often an unrealistic therapeutic choice.

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