Original paper

Specific oral immunotherapy in food allergic patients: transient or persistent tolerance?

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Abstract

Introduction: The first therapeutic choice for food allergy is avoidance of the responsible food, but when this approach is not possible, specific oral desensitization could be considered as a good alternative. It is not clear yet whether the acquired tolerance is transient or persistent.

Aim: We report on a subset of 13 patients of a larger study, treated successfully with specific oral tolerance induction who experienced secondary loss of tolerance after a period of allergen avoidance.

Material and methods: Thirteen patients affected by IgE-mediated food allergy: to cow milk (3 patients), to hen egg (3 patients), to cod fish (2 patients), to peanuts (1 patient) and to corn (1 patient) confirmed by a complete allergological workup and a double-blind placebo-controlled food challenge (DBPCFC), were treated with sublingual-oral desensitization. After the interruption of the maintenance phase, the laboratory tests were performed and 12 of 13 patients underwent DBPCFC.

Results: Oral specific desensitization was completed successfully in all the 13 reported patients. At different times after the end of treatment, they decided, on their own initiative, to stop the ingestion of incriminated food. A new food allergen re-exposure caused adverse reactions in 12 of 13 patients. The detection of specific IgE and IgG4 during the period of allergen avoidance showed an increase in or a stable level of specific IgE and a decrease in specific IgG4 in 8 patients.

Conclusions: According to our experience, the tolerance obtained through the desensitizing treatment is transient and so the regular allergen intake is necessary for its maintenance.

Key words: food allergy, oral specific desensitization, follow-up, allergen avoidance, loss of tolerance, maintenance phase.

Introduction

Food allergy affects 1–4% of the general population [1]. The incidence of food allergy is age dependent, affecting 6% to 8% of children under the age of 3 years and 5% of adult population [2, 3].

The first therapeutic choice for food allergy consists of strict avoidance of the culprit food by elimination diet [4]. This approach is not always possible, especially for basic foods (such as milk or egg), because they have an essential role in psychophysical wellbeing and their complete exclusion from the diet is sometimes very difficult (for example in the case of hidden allergens) [5]. Fortunately, loss of food hypersensitivity may occur in 19–67% of allergic patients within the first 3 to 5 years of life [6].

Some studies showed that the natural history of food allergy changes according to the culprit food; in fact it is common for milk, egg or soy and rare for peanuts, nuts, sesame seeds and fish [7, 8]. In the literature the data are not unambiguous. The study of Skripack suggested that milk allergy is more persistent and children reach a spontaneous tolerance in late childhood or adolescence (64% at 12 years) [9]. Lack reported spontaneous desensitization for the egg, as appropriate in 66% of patients within 5 years of age, 75% – aged 7 years and older, 33% – over 16 years [10]. According to Sampson, spontaneous desensitization occurs only in 20–25% of children with peanut allergy [11]. The Wood's study found that the higher the baseline levels of specific IgE, the smaller is the chance that they can spontaneously reach tolerance [12].

Specific oral desensitizing treatment could be considered a good alternative for those patients who did not acquire clinical tolerance and cannot avoid the ingestion

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of incriminated food. This therapeutic approach has been successfully adopted by several authors [13–19]. In our experience, the oral specific desensitizing treatment is successful in 83.3% of patients who completed the protocol [17]. Analyzing the data of our patients at the end of treatment, we observed a significant decrease in specific IgE and a significant increase in specific IgG4 levels; this appears to be in line with a switch from a Th2 to a Th1 response [15, 18].

Indeed, the OIT immunological mechanisms are still not completely clarified. Low doses of the allergen seem to boost T reg cells inducible (CD25 + FoxP3 +) in the MALT tissue; this leads to a reduced Th2 response due to IL-10 e TGF-β production [20]. Exposure to high doses of the allergen may lead to anergy or clonal deletion of T cells [21].

In both cases it seems that in order to keep such level of tolerance, constant exposure to the allergen should be maintained.

Some authors wondered whether the oral specific desensitization can induce transient or persistent tolerance in patients with food allergy [18, 19, 22, 23]. Most of them think that a regular allergen intake is necessary to maintain the oral tolerance [18, 19, 23]; whereas Staden *et al*. identified a group of children with food allergy (pattern I – responder), who have successfully undergone oral specific desensitization and did not show any allergic symptoms during the reintroduction of incriminated food after a period of avoidance [22].

Aim

Here we report on loss of tolerance in food-allergic patients, who, after successful oral desensitizing treatment, have interrupted the regular allergen intake. In this paper we aim to evaluate the modification of specific IgE and IgG4 values in these patients at the end of desensitization treatment.

Material and methods

We included 13 patients (7 females and 6 males; aged from 4 to 49 years) affected by IgE-mediated food allergy: to cow milk (CM: 5 patients), to hen egg (HE: 3 patients), to cod fish (CF: 2 patients), to peanut (PN: 1 patient), to corn (C: 1 patient) and to apple (A: 1 patient) confirmed by double-blind placebo-controlled food challenge (DBPCFC). All patients were treated with SOTI according to standardized protocols [17, 18]. In the induction phase (IP), the patients underwent SOTI starting with doses diluted in water and then undiluted up to a maximum dose administered (different for each type of food). This was followed by a maintenance phase (MP) with a minimum maintenance dose of 120 ml for CM, 35 g of HE protein (1 egg), 100 g for CF, 40 g for PN, 60 g for C and 180 g for A (1 apple) at least twice a week, plus deliberate additive intake. According to the protocol, all patients, and their parents in the case of children under 18 years of age, were well trained in medical treatment of allergic reactions and equipped with an emergency kit: auto-injectable epinephrine, betamethasone and chlorphenamine and oral second-generation antihistamines (cetirizine, ebastine or loratadine). In the case of any side effects during the IP, the patients could use these therapies. During the IP, 2 patients experienced some mild side effects such as urticaria, angioedema and/or worsening of bronchial asthma so they were treated with oral H_1-antihistamine (cetirizine, ebastine or loratadine).

The laboratory tests (IgE and IgG_{4-} UniCAP System; Pharmacia, Uppsala, Sweden) were performed at the beginning (time 0) and at the end of desensitizing treatment (time 1).

Twelve of 13 patients underwent DBPCFC after the interruption of regular intake of allergenic food.

Results

SOTI was completed successfully in all the 13 reported patients. When stratifying patients on the basis of food allergy, the results can be summarized as follows (Table 1).

Patients with milk allergy (1–5) completed successfully the IP in 4–12 months until the dose of 150 ml; then they continued drinking at least 120 ml of fresh pasteurized milk and eating dairy products as much as they liked with no problems in the maintenance phase (MP: 1–10 months).

In patients 6–8 with egg allergy, the maximum dose (1 egg) was reached in 3–9 months and the intake of one raw egg twice a week plus deliberate intake of meals containing the allergen was continued for 9–15 months of the maintenance phase.

Patients suffering from allergy to cod fish (9–10) became tolerant to the maximum dose (100 g of cod fish) after 8–12 months of treatment, and they continued the maintenance dose (100 g of cod fish 3 times/week) for 6–18 months.

Patient 11 with peanut allergy underwent oral rush desensitization to peanut protein, reaching the maximum dose of peanuts (40 g) after 9 days. She stopped the ingestion of the maintenance dose (40 g of peanuts 4 times/week) after 2 months.

Patient 12 suffering from corn allergy reached the maintenance phase (60 g of corn 3 times/week) in 3 months and that continued for 3 months.

Patient 13 with apple allergy, reached the dose of 180 g of apples after 6 months and he continued it for 12 months.

The patients themselves decided to discontinue the maintenance dose intake and were evaluated after a median of 6 months (minimum 1 month and maximum 12 months) of allergen avoidance.

We decided to repeat allergological evaluation (specific IgE and IgG_4 assessment and DBPCFC). The detec-

Table 1. Description of patients' features

Patient	Age/sex	Allergen	OIT period [months]	Minimum maintenance dose at the end of treatment	Period of allergen avoidance [months]	Cumulative dose-inducing symptoms during DBPCFC	Symptoms following DBPCFC	Therapies
1	18/female	CM	7	120 ml 3 times/week	1	30 ml	UA	Anti-H1
2	20/male	CM	4	120 ml 3 times/week	6	50 ml	UA	CS
3	19/female	CM	4	120 ml 3 times/week	8	50 ml	UA	Anti-H1
4	24/male	CM	12	120 ml 3 times/week	3	10 ml	Dermatitis	Anti-H1
5	4/male	CM	12	120 ml 3 times/week	6	10 ml	GS	NA
6	7/female	HE	9	1 HE 2 times/week	4	7.5 ml	AS	Epinephrine, CS
7	24/male	HE	3	1 HE 2 times/week	1	2 g	Itching, asthma	CS
8	20/female	HE	5	1 HE 2 times/week	2	1 g	UA	CS
9	20/male	CF	8	100 g 3 times/week	12	NA	–	–
10	12/female	CF	12	100 g 3 times/week	2	30 g	UA	Anti-H1
11	49/female	Peanut	< 1	40 g 3 times/week	1.5	100 g	GS	CS
12	36/female	Corn	3	60 g 3 times/week	2	10 g	UA	NA
13	13/male	Apple	6	1 apple 3 times/week	2	87 g	Itching, asthma	CS

CM – cow's milk, HE – hen's egg, CF – cod fish, UA – urticaria/angio-edema, AS – anaphylactic shock, GS – gastrointestinal symptoms, anti-H1 – antihistamine, CS – corticosteroids, NA – not administered.

tion of specific IgE and IgG_4 during the period of allergen avoidance showed an increase in or a stable level of specific IgE and a decrease in specific IgG4 in 8 patients.

DBPCFC was carried out in 12 patients, because one patient developed asthma only after inhalation of fish fumes and the OC was contraindicated. During the DBPCFC, 12 patients presented symptoms ranging from urticaria-angioedema to abdominal pain. In 1 case, a systemic reaction (anaphylactic shock) was observed after the ingestion of 7.5 ml of egg.

Twelve of 13 patients underwent DBPCFC after the interruption of regular intake of allergenic food and in 4 cases, new desensitizing treatment was successfully completed.

Discussion

To date therapeutic strategies in food allergy have been discussed controversially. The gold standard is strict elimination diet, but it is difficult in everyday life and it carries a risk of malnutrition. Furthermore, an elimination diet increases the risk of allergic reactions after accidental ingestion of the culprit food [12, 19]. Therefore, casual treatment is recommended.

The SOTI, in our experience, represents an alternative and safe approach in food allergic patients, who did not spontaneously acquire clinical tolerance and cannot avoid the ingestion of incriminated foods [13, 17, 18, 24].

Whether the induced tolerance is of permanent or transient nature remains unclear. Some authors think, a regular allergen intake is necessary to maintain the established tolerance whereas recently the Nurmatov meta-analysis has led to a huge reduction in the severity of the reactions at the DBPCFC in the active group compared to the control group [18, 19, 23, 25]. Anyway, there are few studies showing the OIT ability to induce permanent tolerance [19, 23, 26, 27].

In this paper we have wanted to focus our attention on the acquired tolerance induced by the desensitization and to show what happened in our 13 patients when they stopped, on their own initiative, the maintenance phase. Although they stopped the intake of incriminated food in different ways at different times, a new allergen re-exposure caused always the return of symptoms in all the 13 reported patients. However, it is interesting to note that the loss of tolerance occurred in patients affected by IgE-mediated allergy to different foods and the different allergenic proteins seem not to influence the natural history of food allergy.

The average age of our patients who discontinued the maintenance dose was 19.5 years, therefore spontaneous desensitization is probability excluded since it typically occurs during the pediatric age.

Moreover, our cases show that the tolerance does not depend on immunotherapy duration or a period of allergen avoidance, but it is bound to the natural history and, most importantly, to the constant exposure to the

allergen. Indeed, if the exposure has not been constant, the immunotherapy effects might be temporary.

Confirming this observation, the DBPCFC, performed in 12 of the 13 patients after the interruption of regular intake of allergenic food, was positive and one of our patient who spontaneously stopped the OIT, after 9-month therapy, had an anaphylactic shock, after the ingestion of culprit food.

One patient did not undergo the second DBPCFC, because he had developed important symptoms only after inhalation or touch of the incriminated food. The changes of allergen-specific IgE and IgG4 have been documented in all the patients. Analyzing the data of our patients at the end of treatment, we observed a significant decrease in specific IgE and a significant increase in specific IgG_4 levels; this appears to be in line with a switch from a Th2 to a Th1 response. The increase in or a stable level of specific IgE and a decrease in specific IgG4 observed in 8 patients could be explained by a return of the switch from a Th1 to a Th2 response.

Although we believe it will be necessary to perform more in-depth studies on the causes concerning the loss of tolerance, we conclude that SOTI does not alter the natural outcome of food allergy. It substantially induces the increase in the threshold dose necessary to elicit allergic symptoms, resulting in transient clinical tolerance. Until now, only little information has been available on the dosage intervals to preserve the acquired tolerance [28].

Therefore, a regular allergen intake is necessary for its maintenance.

According to our experience, for safety reasons, the intake of culprit food should be recommended at least twice a week plus deliberate intake of meals containing the allergen.

The OIT decreases the risk of allergic reactions in patients with severe food allergy, allows culprit food reintroduction and consequently life quality improvement, but the OIT main pitfall is the lack of standardized protocols.

Conclusions

Further trials are needed to create OIT standardized protocols in order to boost security and to identify biomarkers defining the patients that are in danger.

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Conflict of interest

The authors declare no conflict of interest.

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