

Short communication

Specific oral tolerance induction with food in children: transient or persistent effect on food allergy?

Background: The standard treatment of food allergy is elimination of the incriminated food from the diet. Specific oral tolerance induction (SOTI) seems to be a promising approach for a causal treatment; however, it is unclear whether the tolerance achieved is transient or persistent. We report on a subset of three patients of a larger ongoing study who were treated successfully with SOTI treatment, but experienced a secondary loss of tolerance after a period of allergen avoidance.

Methods: The patients suffered from IgE-mediated allergy either to cow's milk (CM) (patient A) or hen's egg (HE) (patients B and C), confirmed by double-blind, placebo-controlled food challenge (DBPCFC). SOTI treatment was performed at home on a daily basis until tolerance to a maximum of 250 ml CM or 4.5 g lyophilized HE protein was achieved. The daily maintenance dose was 100 ml CM or 2.5 g HE protein.

Results: Patients A, B and C reached tolerance to the maximum dose after 37, 41 and 52 weeks, respectively. According to the protocol, patients A and B performed a strict secondary elimination diet for 2 months prior to a follow-up DBPCFC after a maintenance phase of 27 and 39 weeks, respectively. Patient C discontinued treatment for 2 days after 4 weeks on the maintenance dose. Despite previous tolerance, on re-exposure to the allergen all patients experienced moderate systemic allergic reactions.

Conclusions: We conclude that SOTI can induce transient tolerance in food allergy, but does not necessarily lead to its permanent abrogation. Regular allergen intake seems necessary to maintain the established tolerance.

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Today, the treatment of choice for IgE-mediated food allergy is avoidance of the incriminated food by elimination diet (1). Especially for basic foods such as cow's milk (CM) or hen's egg (HE) this is sometimes difficult because of their widespread use in processed food (1). As a consequence dietary failures are frequent and may lead to severe allergic reactions. A causal therapy for the treatment of food allergy is therefore highly warranted.

Preliminary experience with specific oral tolerance induction (SOTI) to foods, especially CM, seems promising and reports have been published with limited number of patients in the 1970s and in some more recent studies (2, 3). In one of these, Patriarca et al. (2) treated a subset of 29 adults and children with IgE-mediated CM allergy and 15 with HE allergy, with increasing daily doses up to a maintenance dose of 120 ml CM or the equivalent of one egg, over a period of 3–12 months. Clinical tolerance was achieved in 79% of patients with

CM and 85% with HE allergy. The other patients experienced recurrent symptoms at lower doses and did not complete the protocol. Meglio et al. (3) reported similar efficacy of SOTI, demonstrating that 71% of 21 CM-allergic children tolerated 200 ml CM after a 6-month treatment period.

However, no information is available, whether the tolerance achieved is transient or persistent. Therefore, one cannot predict the risk of irregular allergen exposure after acquired tolerance, a crucial point for the patient's advice. We are currently conducting a SOTI study in children with CM or HE allergy. Here we preliminarily report on a subset of three of these patients who had a successful SOTI treatment but suffered a secondary loss of tolerance after a period of allergen avoidance.

Methods

The three patients suffered from IgE-mediated food allergy since their first year of life, confirmed by double-blind, placebo-controlled food challenge (DBPCFC) to either CM (patient A; Fig. 1) or HE

Abbreviations: CM, cow's milk; DBPCFC, double-blind, placebo-controlled food challenge; HE, hen's egg; IgE, immunoglobulin E; SOTI, specific oral tolerance induction.

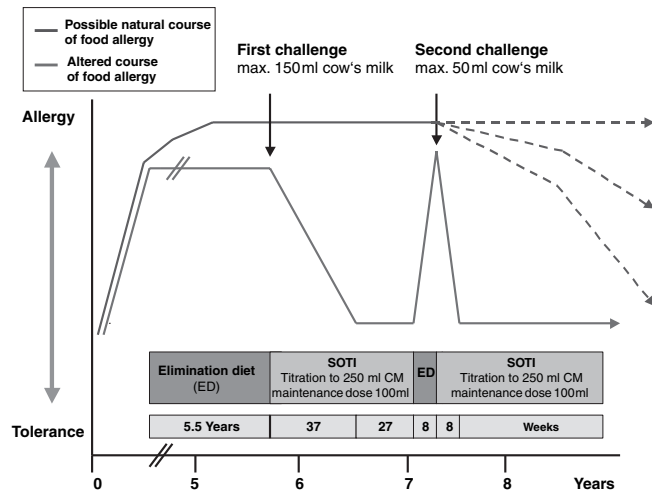


Figure 1. The natural and altered course of food allergy for patient A during elimination diet, SOTI and oral food challenges.

(patients B and C). The patients were challenged in order to confirm that their allergy was still of clinical relevance (Table 1) as published elsewhere (4). Then, the patients were treated with SOTI either with CM or HE at home on a daily basis starting with 0.0006 ml CM or 0.01 mg HE protein, respectively, increased to a maximum dose of 250 ml CM or 4.5 g lyophilized HE protein, until tolerance was achieved. The minimum daily maintenance dose was 100 ml CM or 2.5 g HE protein (1/2 egg) plus deliberate additive intake.

The SOTI protocol was handed out after comprehensive explanation to patients and their parents indicating the suggested increase in doses for each day. According to the protocol, the administration during the induction phase had to be preceded and followed by a 2-h interval to any other food ingestion. All persons were well trained in medical treatment of allergic reactions and equipped with the respective drugs. The parents were instructed to initiate communication over the telephone with the study

investigator within 24 h to discuss the consecutive doses in case of any symptoms following the SOTI treatment.

Results

The three reported patients had to extend the intended SOTI induction phase of 9 weeks as a result of minor allergic symptoms at different doses. Patient A reached the maximum dose of CM after 37 weeks and then continued the maintenance dose for 27 weeks (Fig. 1). According to our study protocol, he then received a strict secondary elimination diet for 2 months prior to a follow-up DBPCFC, during which he experienced acute urticaria within 15 min at a cumulative dose of 50 ml CM. Back on SOTI he re-acquired tolerance again within 8 weeks.

Patient B needed 41 weeks to tolerate the maximum dose of HE and continued the intake during a 39-week maintenance phase. After the elimination diet for 2 months patient B developed acute urticaria and rhinoconjunctivitis within 10 min after a cumulative dose of 0.66 g HE protein during the follow-up DBPCFC. Thereafter, SOTI was successfully initiated again.

Patient C suffered from severe HE allergy and became tolerant to the maximum dose after 52 weeks of SOTI. However, he continued to complain of transient itching lips for several minutes after intake. Four weeks after reaching the maintenance dose he discontinued HE intake for 2 days due to compliance problems. On re-exposure to the maintenance dose on day 3, he developed a generalized urticaria and swelling of the lips 20 min after ingestion. He repeated the intake on day 4, experiencing less severe swelling of the lips and no urticaria, and thereafter continued according to the protocol.

Table 1. Patient characterization

	Patient A		Patient B		Patient C
	1st DBPCFC	2nd DBPCFC	1st DBPCFC	2nd DBPCFC	1st DBPCFC
Allergen	Cow's milk	Cow's milk	Hen's egg	Hen's egg	Hen's egg
Age (years, months)	5.8	7.4	4.9	6.7	12.9
Time from DBPCFC ingestion (last dose) to symptoms (min)	10–15	10–15	5–10	5–10	5–10
Specific IgE (kU/l)*	10.9	3.8	6.9	2.0	23.3
Skin prick test [allergen (mm)/histamine (mm)]*	11/5	7/6	15/6	12/6	13/5
Atopy patch test*	Negative	Negative	Positive	Negative	Negative
Further allergies (symptoms and sIgE)	Hen's egg, peanut	Hen's egg, peanut	Kiwi, birch, dog, cat and horse dander	Kiwi, birch, dog, cat and horse dander	Hazelnut, carrot, kiwi, pollen, dust mite, dog and cat dander
Cumulative dose-inducing symptoms	150 ml cow's milk	50 ml cow's milk	0.20 g hen's egg protein	0.66 g hen's egg protein	0.013 g hen's egg protein
Symptoms following DBPCFC	Generalized urticaria, angio-oedema, rhinitis	Generalized urticaria	Generalized urticaria	Generalized urticaria, rhinoconjunctivitis	Generalized urticaria, swollen lips

*Concerning the respective allergen.

Discussion

This preliminary report on three patients is part of a larger ongoing SOTI study. These three case reports indicate that SOTI can induce oral tolerance in food allergy, which is not necessarily of persistent nature. We therefore speculate that SOTI does not alter the natural outcome of food allergy, but substantially increases the threshold dose necessary to elicit allergic symptoms, resulting in clinical tolerance in a large number of patients. However, in the absence of daily allergen intake during a secondary elimination diet the threshold dose is likely to decrease again, as demonstrated in our patients.

We hypothesize that this phenomenon depends on a number of variables, such as the basic threshold dose, the duration of SOTI, of elimination diet, and the patient's individual course of disease. Therefore, in

patients with a small likelihood of natural remission of the food allergy, regular long-term treatment might be necessary. Until now, only little information was available on the dosage intervals needed in the maintenance phase to preserve the acquired tolerance (5); our cases indicate that for safety reasons a daily intake should be recommended.

The advantages of the SOTI treatment are a dramatic reduction in the risk of severe allergic reactions at least in some patients with intense food allergy to CM or HE and the possibility of introducing these foods to the patient's diet results in an improvement in the patient's quality of life. Further studies are warranted to better characterize patients with high susceptibility to effective SOTI treatment, and to delineate the required time-frames, and immunologic markers to monitor the course.

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