

Original article

Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction

Background: Specific oral tolerance induction (SOTI) seems to be a promising treatment of food allergy. Specific oral tolerance induction and elimination diet were compared with respect to efficacy rate and patterns of clinical reaction.

Methods: Children with challenge proven immunoglobulin E (IgE)-mediated cow's milk (CM) allergy or hen's egg (HE) allergy were randomly assigned to SOTI or elimination diet as a control group. Specific oral tolerance induction treatment was performed at home on a daily basis according to a study protocol with fresh CM or lyophilized HE protein. Re-evaluation of clinically relevant food allergy was performed by food challenge after a median of 21 months. Children in the SOTI group received a secondary elimination diet for 2 months prior to follow-up challenge to evaluate persistence of induced oral tolerance.

Results: At follow-up challenge, nine of 25 children (36%) showed permanent tolerance in the SOTI group, three of 25 (12%) were tolerant with regular intake and four of 25 (16%) were partial responders. In the control group, seven of 20 children (35%) were tolerant. Allergen-specific immunoglobulin E decreased significantly both in children who developed natural tolerance during the elimination diet ($P < 0.05$) and in those with SOTI ($P < 0.001$).

Conclusions: Specific oral tolerance induction seems a valid treatment option for patients with persistent food allergy. Indications may be given if avoidance cannot be guaranteed or for those who are eager to eat the food in question. Advantages of SOTI are the increased threshold dose for allergic reactions and the substantially reduced risk of severe allergic reactions after inadvertent ingestion of the allergen. However, careful monitoring during SOTI is mandatory.

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Key words: children; food allergy; specific oral tolerance induction.

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Accepted for publication 23 June 2007

The prevalence of food allergy is increasing. Around 2–3% of adults and up to 6% of children suffer from food allergy (1–5). To date, the only generally accepted therapy is a strict elimination diet. For common foods such as cow's milk (CM) or hen's egg (HE), avoidance is difficult in everyday life. Under elimination diet, patients have a high risk of severe allergic reactions in the case of accidental ingestion (6, 7). The most common identifiable cause of anaphylactic reactions is food allergy (8, 9). There is a need for causal therapeutic strategies.

Specific oral tolerance induction (SOTI) achieved by oral exposure to increasing doses of the specific food allergen seems to be a promising causal approach to therapy, improving both quality of life and safety in the event of accidental ingestion of the offending food (10).

Preliminary experience with SOTI in food allergy shows efficacy rates of 75–86% for CM and HE (11–14). Despite the clear need for a causal treatment for food allergy, certain scepticism towards SOTI remains, because of the risk of side-effects and the lack of sufficiently large controlled studies.

We investigated children with food allergy to CM or HE who were randomly assigned to either an elimination diet (control group) or SOTI (treatment group) and compared these with respect to efficacy rates for oral tolerance. Furthermore, patterns of reaction during SOTI were characterized to evaluate how patients profit best from SOTI.

Methods

Study population and study protocols

We included 47 children with immunoglobulin E (IgE)-mediated food allergy to either CM or HE confirmed by double-blind, placebo-controlled food challenge (DBPCFC). Children were recruited

Abbreviations: CM, cow's milk; DBPCFC, double-blind, placebo-controlled food challenge; ED, eliciting dose; HE, hen's egg; IgE, Immunoglobulin E; IP, induction phase; MP, maintenance phase; SCORAD, scoring atopic dermatitis; sIgE, specific Immunoglobulin E; SOTI, specific oral tolerance induction.

at the Department of Pediatric Pneumology and Immunology, Children's Hospital Charité, Berlin and the Children's Hospital Osnabrück. There were two drop-outs; one child in the control group (CM) was lost during follow up and a child in the treatment group (HE) did not start SOTI. Therefore, 45 children were followed throughout the study (29 boys, 16 girls; median age 2.5 years, range 0.6–12.9 years); 27 patients were recruited in Berlin and 18 patients in Osnabrück. Sixty percent (27/45) children had mild to moderate atopic dermatitis (14 patients in the SOTI group and 13 patients in the control group). Severe atopic dermatitis with a seventy scoring of atopic dermatitis (SCORAD) above 75 (15) was an exclusion criterion.

Patients were randomly assigned to SOTI (treatment group) or the elimination diet (control group). Evaluation of the two different treatment strategies was performed by a follow-up food challenge and planned after 18–24 months. Children on SOTI received a secondary strict elimination diet 2 months prior to the follow-up food challenge to evaluate persistence of induced oral tolerance. According to the study protocol, in the induction phase (IP), children with CM and HE allergy underwent SOTI with 3.5% fresh pasteurized CM or lyophilized HE protein at home on a daily basis starting with an equivalent of 0.02 mg CM protein or 0.006 mg HE protein. Doses were increased according to the individual tolerance to a maximum dose of 8250 mg CM protein (250 ml CM) or 2800 mg HE protein (around ½ HE). This was followed by a maintenance phase (MP) with a minimum daily maintenance dose of 3300 mg CM protein (100 ml CM) and 1600 mg HE protein (around ¼ HE) plus deliberate intake. The planned duration for the IP for both CM and HE was 67 days. In case of any side-effects, additional steps with smaller increase of the dosage were added and the single steps performed at a slower pace. The IP for CM and HE

Table 1. Scheme for the Specific oral tolerance induction induction phase with cow's milk

Concentration: milk : water	Day	Quantity	CM protein (mg)
1 + 99 ml	1	1 drop	0.02
	2	2 drops	0.03
	3	3 drops	0.05
	4	4 drops	0.07
	5	5 drops	0.08
	6	6 drops	0.10
	7	7 drops	0.12
	8	8 drops	0.13
	9	9 drops	0.15
	10	10 drops	0.17
	11	14 drops	0.23
	12	20 drops	0.33
1 + 9 ml	13	3 drops	0.50
	14	4 drops	0.66
	15	5 drops	0.83
	16	6 drops	1.0
	17	7 drops	1.2
	18	8 drops	1.3
	19	10 drops	1.7
	20	14 drops	2.3
	21	20 drops	3.3
Pure milk	22	3 drops	5.0
	23	4 drops	6.6
	24	5 drops	8.3

Table 1. (Continued)

Concentration: milk : water	Day	Quantity	CM protein (mg)
	25	6 drops	10.0
	26	7 drops	11.5
	27	8 drops	13.2
	28	10 drops	16.5
	29	14 drops	23.1
	30	20 drops	33
	31	2.5 ml	83
	32	2.75 ml	91
	33	3 ml	99
	34	3.5 ml	116
	35	4 ml	132
	36	5 ml	165
	37	6 ml	198
	38	8 ml	264
	39	12.5 ml	413
	40	13 ml	429
	41	14 ml	462
	42	15 ml	495
	43	16 ml	528
	44	17 ml	561
	45	18 ml	594
	46	19 ml	627
	47	20 ml	660
	48	22.5 ml	743
	49	25 ml	825
	50	27.5 ml	908
	51	30 ml	990
	52	35 ml	1155
	53	40 ml	1320
	54	50 ml	1650
	55	65 ml	2145
	56	85 ml	2805
	57	105 ml	3465
	58	125 ml	4125
	59	140 ml	4620
	60	150 ml	4950
	61	160 ml	5280
	62	170 ml	5610
	63	180 ml	5940
	64	190 ml	6270
	65	210 ml	6930
	66	225 ml	7425
	67	250 ml	8250

is shown in Tables 1 and 2. The following MP was reduced according to the duration of the IP.

The SOTI protocol was given to parents after thorough explanation. During the IP, the child had to be under observation for 3 h after intake of the allergen. Parents were trained in medical treatment of allergic reactions and were provided with appropriate drugs. They were also instructed to phone the study physicians in the event of any allergic reaction to discuss subsequent doses.

Different patterns of clinical reaction

Patients in the SOTI or elimination group were categorized according to their clinical patterns of reaction during SOTI and their clinical reactions in the follow-up food challenge.

Table 2. Scheme for the Specific oral tolerance induction induction phase with lyophilized hen's egg powder

Day	Concentration (mg/ml)	HE-powder (mg)	H ₂ O (ml)	Quantity	HE-protein (mg)
1	0.05	5	100	3 drops	0.006
2	0.05	5	100	4 drops	0.008
3	0.05	5	100	6 drops	0.012
4	0.05	5	100	10 drops	0.020
5	0.05	5	100	12 drops	0.024
6	0.05	5	100	14 drops	0.028
7	0.05	5	100	16 drops	0.032
8	0.05	5	100	19 drops	0.038
9	0.2	10	50	5 drops	0.040
10	0.2	10	50	7 drops	0.056
11	0.2	10	50	9 drops	0.072
12	0.4	20	50	7 drops	0.112
13	0.4	20	50	14 drops	0.224
14	1	50	50	6 drops	0.24
15	1	50	50	7 drops	0.28
16	1	50	50	8 drops	0.32
17	1	50	50	9 drops	0.36
18	1	50	50	11 drops	0.44
19	0.5	50	100	1.75 ml	0.7
20	0.5	50	100	2.25 ml	0.9
21	0.5	50	100	3.5 ml	1.4
22	0.5	50	100	7 ml	2.8
23	0.5	50	100	8 ml	3.2
24	0.5	50	100	9 ml	3.6
25	0.5	50	100	10 ml	4.0
26	0.5	50	100	11.5 ml	4.6
27	0.5	50	100	14 ml	5.6
28	1	100	100	8.5 ml	6.8
29	1	100	100	12 ml	9.6
30	1	100	100	17.5 ml	14.0
31	4	200	50	8.5 ml	27.2
32	4	200	50	10 ml	32.0
33	4	200	50	11 ml	35.2
34	4	200	50	12.5 ml	40.0
35	4	200	50	15 ml	48
36	4	200	50	17.5 ml	56
37	10	500	50	8.5 ml	68
38	10	500	50	12 ml	96
39	10	500	50	17.5 ml	140
40	10	500	50	18.5 ml	148
41	10	500	50	19.5 ml	156
42	10	500	50	20.5 ml	164
43	10	500	50	22 ml	176
44	10	500	50	23.5 ml	188
45	10	500	50	25 ml	200
46	20	1000	50	13.5 ml	216
47	20	1000	50	14.5 ml	232
48	20	1000	50	16 ml	256
49	20	1000	50	17.5 ml	280
50	20	1000	50	19.5 ml	312
51	20	1000	50	22 ml	352
52	20	1000	50	25 ml	400
53	20	1000	50	30 ml	480
54	20	1000	50	35 ml	560
55	20	1000	50	45 ml	720
56	40	2000	50	30 ml	960
57	40	2000	50	44 ml	1408
58	40	2000	50	46 ml	1472
59	40	2000	50	48 ml	1536

Table 2. (Continued)

Day	Concentration (mg/ml)	HE-powder (mg)	H ₂ O (ml)	Quantity	HE-protein (mg)
60	50	2500	50	41 ml	1640
61	50	2500	50	44.5 ml	1780
62	50	2500	50	46.5 ml	1860
63	50	2500	50	50 ml	2000
64	60	3000	50	45 ml	2160
65	70	3500	50	42 ml	2352
66	70	3500	50	46 ml	2576
67	70	3500	50	50 ml	2800

SOTI group (Fig. 1)

Pattern I (responder): children who were tolerant in the follow-up DBPCFC after the secondary elimination diet.

Pattern II (responder – with regular intake): children who were tolerant with daily maintenance dose, but showed allergic symptoms after a period of avoidance.

Pattern III (partial responder): children tolerated a lower dosage of the allergen food than the planned full maintenance dosage. However, an increased dosage always resulted in clinical symptoms.

Pattern IV (non-responder): SOTI had to be stopped because the increasing titration steps of the respective SOTI protocol were repeatedly not tolerated by patients at the early steps of the protocol.

Elimination diet (control group)

Elimination responder: children who developed natural tolerance and therefore had a negative follow-up food challenge.

Elimination non-responder: children still demonstrated signs of relevant food allergy during follow-up food challenge.

Determination of IgE antibodies

Blood sample was drawn prior to start of the intervention, prior to re-challenges or at final examination. Patient serum was analyzed

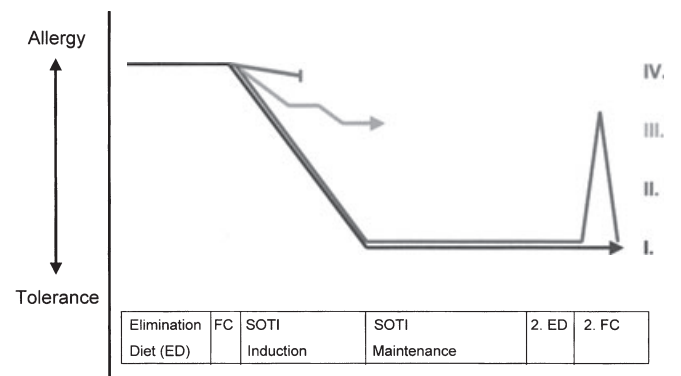


Figure 1. The four clinical patterns of reactions observed during specific oral tolerance induction (SOTI) treatment. ED: elimination diet, FC: food challenge.

for concentrations of total IgE and specific immunoglobulin E (sIgE) to CM and HE using the Phadia CAP-System FEIA® (Phadia-Diagnostics, Uppsala, Sweden). Lower detection limit of the CAP-System was 0.35 kU/l; in the case of levels above 100 kU/l serum was diluted.

Oral food challenges

Clinical reactivity to CM or HE was investigated by DBPCFC as described in detail previously (16). In brief, patients received placebo or verum on two different days. The clinical dietician performed the randomization and preparation of the challenges. A maximum of seven gradually increasing titration steps were given at intervals of 30 min up to a maximum dose of 3300 mg of CM protein (fresh, pasteurized, 3.5% fat containing CM, 3.3 g/100 ml of CM protein) or 4600 mg of HE protein (raw HE white and yolk, Berlin or lyophilized HE powder, Osnabrück). The cumulative dose during DBPCFC was 4770 mg CM protein or 6200 mg HE protein if no reaction was observed. Placebo was based on either Neocate® (SHS, Liverpool, UK) or Sinlac® (Nestlé, Germany, Frankfurt).

Provocation was stopped if clinical symptoms were observed or the highest dose was reached. Symptoms were scored by a paediatric allergy specialist and the challenge was assessed as positive when objective symptoms occurred, such as urticaria, exacerbation of eczema (at least 10 point increase in SCORAD score), angioedema, wheezing, allergic rhinitis or conjunctivitis, vomiting, diarrhea, or shock.

Statistics

The Wilcoxon test was used to evaluate whether there was a significant change in total- or allergen-sIgE (kU/l) comparing the respective values after intervention (SOTI or elimination diet) with those at the beginning of the study (first food challenge). Mann-Whitney test was used to test for differences between groups. The chi-squared test was used to compare the proportion of tolerance development in the SOTI and control group. Statistical significance was defined by a two-sided alpha-level of 0.05. All analyses were performed with SPSS for Windows (version 14.0, SPSS Inc., Chicago, IL, USA).

Results

Tolerance development during SOTI and elimination diet

Forty-five children were followed. Twenty-five patients were randomized in the SOTI group (CM: $n = 14$; HE: $n = 11$) and 20 patients in the elimination group (CM: $n = 10$; HE: $n = 10$). Fourteen of the 25 children in the SOTI group completed the IP in a period between 70 days and 12 months. Additional two children had an extremely slow IP (28 and 46 months) because of recurrent infections or allergic rhinoconjunctivitis during pollen season. In nine patients, the induction was not completed because of recurrent side-effects (non-responder). The overall median duration for the IP was 7 months. The following MP ranged from 7 to 15 months (median 9 months) and was reduced according to the duration of the IP. Altogether, oral tolerance for all children was finally evaluated after a median of 21 months (minimum 11 months and maximum

Table 3. Specific oral tolerance induction (SOTI) patterns and tolerance rates during SOTI or elimination diet

SOTI-group ($n = 25$)			Control-group ($n = 20$)	
Pattern		n (%)	Result	n (%)
I	Responder (natural course or SOTI?)	9 (36)	Tolerant	7 (35)
II	Responder (with regular daily intake)	3 (12)		
III	Partial responder	4 (16)		
IV	No responder	9 (36)	Allergic	13 [65%]

59 months). Matching this, children in the control group were evaluated after a median of 21 months (minimum 12 months and maximum 47 months).

Allocation to the different SOTI patterns and tolerance rate are shown in Table 3. With SOTI treatment, 16/25 children (64%) were able to integrate the allergenic food in the diet, nine with permanent tolerance (pattern I) and seven with partial tolerance (patterns II + III). In contrast, in the control group, only seven of 20 children (35%) were tolerant ($P = 0.05$).

Total and allergen-sIgE during SOTI and elimination diet

On inclusion in the study, no differences were observed in allergen-sIgE levels (CM or HE) between patients randomized in the SOTI or control group (Fig. 2). Allergen-sIgE decreased significantly over time in children who developed their natural tolerance under elimination diet as expected ($P < 0.05$; Fig. 3B). Under intervention with SOTI, children in the responder group and partial responder groups (patterns I–III) showed a similar response ($P < 0.001$; Fig. 3A). There was no significant change in sIgE in children who had to stop SOTI (pattern IV, non-responder) and the ones who were non-responders under elimination diet. Children in the SOTI group who

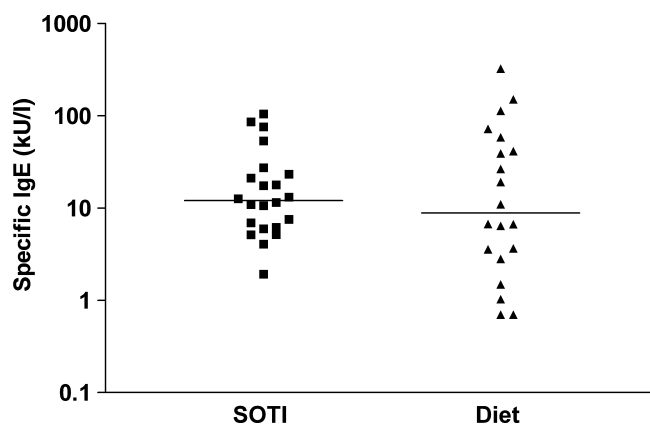


Figure 2. Level of allergen-specific serum IgE (cow's milk or hen's egg) for patients randomized into the specific oral tolerance induction (SOTI) or control group on enrolment into the study.

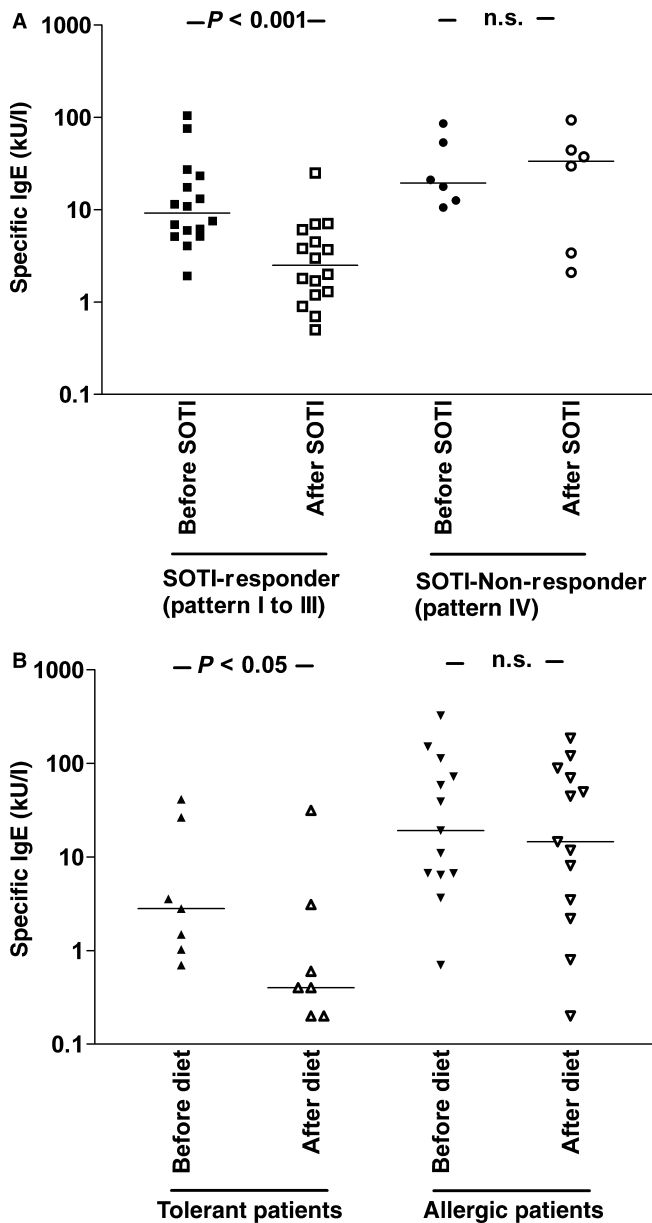


Figure 3. Allergen-specific serum IgE (cow's milk or hen's egg) over time during specific oral tolerance induction (SOTI) (A) or elimination diet (B). Results are shown for two different groups each, in SOTI responder and non-responder or in the control group tolerant and intolerant patients.

were responders had lower sIgE levels than the non-responders at the beginning of the study ($P < 0.05$). With respect to total IgE there was no significant alteration in values for either SOTI or elimination group (data not shown).

Adverse reactions during SOTI and elimination diet

Side-effects are shown in Table 4. All children in the SOTI group had side-effects to some extent. Twenty-one children presented with mild symptoms, such as single wheals,

Table 4. Adverse reactions during Specific oral tolerance induction (SOTI) or under elimination diet

Reactions	SOTI (n)	Elimination diet (n)
No adverse reactions	0	14
Skin reactions		
Exacerbation of eczema	13*,‡	2†
Urticaria	11*	3†
Angioedema	4*	0
GI symptoms		
Tingling in the mouth	3*	0
Nausea	6*	1†
Vomiting	6*	2†
Respiratory symptoms		
Wheezing	2*,§	0
Rhinoconjunctivitis	2*	0
Cardiovascular symptoms	0	1†,¶

*In all cases reactions occurred during the 3-h observation time after intended ingestion.

†All reactions occurred after accidental ingestion of the avoided allergenic food.

‡In three cases termination of SOTI because of exacerbation of eczema.

§All children with respiratory problems had a known bronchial asthma.

¶Child had an immediate reaction after accidental ingestion with vomiting, paleness and circulation disorder.

tingling sensation in the mouth, nausea, or deterioration of the eczema, which were easily controlled by oral antihistamines if needed. In four children, the side-effects during SOTI were moderate with generalized urticaria, bronchial obstruction, or angioedema, which were successfully treated with antihistamines and steroids. Twelve of 25 patients had lower threshold doses because of 'augmentation factors'. The most common 'augmentation factors' were infection, exercise, pollen allergy, or irregular intake. The intermittent reduction in the dose prevented further allergic reactions after the intake.

In the control group, five children had mild to moderate side-effects because of inadvertent ingestion of the allergen (Table 3). One child had severe side-effects after accidental ingestion presenting with vomiting, paleness and circulation disorder. Fourteen children had no accidental ingestion of the eliminated allergen and were without reactions during elimination. Two children in the elimination group were at high risk of severe allergic reactions and were equipped with an adrenalin self-administration-pen. Both children showed more severe allergic signs in the follow-up DBPCFC, with symptoms, such as bronchial obstruction, generalized urticaria, and circulatory disorders.

Case reports of different patterns during SOTI

Children in the SOTI group were classified according to the four clinical patterns. Each pattern is outlined by a short case report of one to two patients.

Pattern I (responder – natural course or SOTI?) includes those children who were tolerant in the follow-up DBPCFC after the secondary elimination diet. There-

fore, tolerance in these children is defined as permanent tolerance.

Patient KM, aged 11.2 years, HE allergy, eliciting dose (ED) at first DBPCFC: 460 mg HE protein, IP: 70 days, MP: 395 days. He had some mild side-effects during IP and MP, such as mild allergic rhinoconjunctivitis or single wheals without the need for medical intervention. More than half of these episodes occurred during an infection. During IP, the dose could not be increased for a few days. Afterwards, there was no need for a change in the dosage. After a secondary elimination diet the patient had a negative follow-up oral challenge and therefore reached permanent oral tolerance for HE.

Patient JB: age 2.9 years, CM allergy, ED at first DBPCFC: 99 mg of CM protein, IP: 177 days, MP: 318 days. She had several episodes with mild side-effects, which sometimes required antihistamines. Most of the episodes occurred during an infection, requiring a mild reduction of the dose for a few days.

Pattern II (responder – with regular intake): patients in this group were tolerant, but showed allergic symptoms after a period of avoidance.

Patient FK: age 5.8 years, CM allergy, ED at first DBPCFC 3300 mg of CM protein, IP: 312 days, MP: 207 days. The patient had mild side-effects (worsening eczema, stomach ache, and mild urticaria). Antihistamines were used occasionally. At the follow-up food challenge, the patient reacted at a lower ED of 990 mg of CM protein. Re-SOTI was uneventful; IP took 56 days. Since then he has been on the maintenance dose, occasionally leaving out the milk for 1 or 2 days. A second follow-up food challenge after elimination diet was refused because of negative experience during the first follow-up challenge.

Pattern III (partial responder): children tolerated a dosage of the allergenic food lower than the planned full maintenance dosage. However, an increased dosage always resulted in clinical symptoms.

Patient MW: 12.9 years, HE allergy, ED at first DBPCFC 14 mg of HE protein. He reached the maintenance dose after 356 days. Side-effects were mild, mainly consisting of an itching sensation in the mouth for several minutes after intake of HE powder. After 4 weeks on MP, the patient stopped HE intake for 2 days because of compliance problems. On re-exposure of 2000 mg of HE protein he experienced generalized urticaria and swelling of the lips. He repeated the same dose on the next day and developed mild swelling of the lips but no urticaria. Dose was reduced to 400 mg over several months and then gradually increased up to a maximum dose of 800 mg over 14 months. During an unstable phase, augmentation factors, such as an infection, exercise within 1 or 2 h after intake of HE protein or break in intake of 1 or 2 days were followed by symptoms, such as moderate to generalized urticaria with swelling of the lips and eyelids. Oral medication with antihistamines and steroids were needed on four occasions. The patient wanted to continue

the treatment and compliance has improved. He avoids exercise after ingestion of HE protein and during an infection he takes a decreased dosage when experiencing mild side-effects. Now he is stable on a dose of 1000 mg of HE protein.

Pattern IV (nonresponder): The titration procedure of the SOTI protocol was not tolerated by patients and therefore SOTI had to be stopped at the early steps of the protocol.

Patient BA: 3.6 years, CM allergy, ED at first DBPCFC 13 mg of CM protein. Dosage could slowly be increased up to a maximum of 330 mg of CM protein after 3 months. Specific oral tolerance induction was stopped because of recurrent episodes of vomiting.

Patient PM: 2.9 years, HE allergy, ED at first DBPCFC 5 mg of HE protein. Specific oral tolerance induction was stopped after 6 weeks because of worsening of the eczema.

Discussion

Therapeutic strategies in food allergy are discussed controversially. To date, the gold standard is strict elimination diet (17). However, this method may have disadvantages. Strict avoidance is difficult in everyday life and has the risk of malnutrition. Furthermore, an elimination diet may even increase the chance for developing allergic reactions after accidental ingestion as shown by a recent study in children with atopic dermatitis and sensitization to CM under prolonged elimination diet (6). Food allergens are the most frequent reason for anaphylactic reactions (8, 9). Therefore, a causal treatment is desirable. Subcutaneous injection immunotherapy is not recommended for food allergy because of an unacceptably high rate of severe side-effects (18, 19). Treatment with anti-IgE injection increased threshold doses for allergenic responses in the majority of patients with peanut allergy (20). However, around 25% of patients did not experience an improvement. Moreover, anti-IgE therapy requires frequent administration to maintain the IgE-deficient state and is rather expensive.

Preliminary experience with studies on oral tolerance induction has shown promising results with efficacy rates between 75% and 86% (11–14, 21). Yet, SOTI meets with some scepticism because of lack of large controlled studies and the risk of side-effects. In the present study, efficacy rates for the elimination diet (control group) and SOTI (treatment group) were compared over a median time period of 21 months. To date, there has only been one controlled study with SOTI. Patriarca et al. (13) showed in their study that 83% of the children in the SOTI group became tolerant after 18 months whereas all children under elimination diet had a positive DBPCFC. The authors argued that this rules out spontaneous desensitization. Whether the induced tolerance was of permanent or transient nature remained unclear. Our

results showed the same efficacy rates for permanent tolerance in the SOTI group (36%) and in the elimination group (35%). However, including children who reached partial tolerance increased the efficacy rate to 64%. This group would include patients who need a regular intake of the allergen to maintain tolerance or those who can tolerate a dosage lower than the standard maximum dose. Similar cases of partial tolerance have been reported in the literature (12, 14).

Children who reach partial tolerance have a substantially increased quality of life because the offending food can be integrated in their diet. Far more importantly, the child is protected against potentially fatal allergic reactions through accidental intake of small amounts of the allergen. Thus, SOTI may not alter the natural course of tolerance development but substantially increases the threshold dose necessary to elicit allergic reactions.

In addition, with SOTI there is a high chance that children reach their maintenance dose after some months, compared with the follow-up challenge usually after 1.5 years in case of elimination diet. In our study, children reached maintenance dose after a median of 7 month with the corresponding advantages. In these respects, SOTI is superior to elimination diet. At the same time, children with partial oral tolerance seem to require regular intake to maintain the established tolerance. This has been reported before by our group and other authors (7, 22, 23).

In the literature on SOTI, side-effects are reported in 50–60% of cases (13, 14). This is in contrast to our experience, that all children in the SOTI group experienced side-effects to some extent. This difference might be explained by the fact that our patients did not receive oral antihistamines on a regular basis in order not to mask any allergic reaction. In all cases, side-effects were mild to moderate. Mild side-effects ranged from itching sensation in the mouth and nausea to single wheals and were easily controlled by antihistamines if needed. In four of 25 children in the SOTI group, moderate side-effects occurred with generalized urticaria, wheezing or angioedema. Oral therapy with antihistamines and steroids were sufficient to control symptoms. Severe side-effects were not observed. Moreover, all side-effects occurred after known exposure to the allergen and patients were prepared. In contrast, one severe allergic reaction occurred in the control group after accidental ingestion of the food.

In general, SOTI requires careful and continuous medical supervision by an experienced allergologist. Parents and children need comprehensive medical emergency training for allergic reactions and equipment with the relevant drugs. Especially in combination with augmentation factors, there is an increased risk for side-effects in some patients. Our patients had a reduced threshold for allergic reactions mainly during an infection. One teenager experienced generalized urticaria and angioedema after taking his regular HE protein, then

eating a ready-to-serve meal that contained HE and immediately afterwards going for a long training session. In other patients, a trigger factor was pollen allergy. Dose reduction, however, always prevented side-effects. Consequently, exercise should be avoided in the hours after ingestion of the allergen, as recommended by others (24, 25). During an infection or in the pollen season, the dosage should be reduced, particularly in children whose immunological reactivity threshold is low, such as partial responders.

The underlying immunological mechanisms remain to be clarified and may help improve efficacy rates of SOTI. In the present study, development of tolerance was associated with a significant reduction in sIgE. Specific IgE decreased significantly in those children who developed their natural tolerance while on an elimination diet as described previously (26). Simultaneously, there was a significant reduction in sIgE under the regime of SOTI in children who developed permanent tolerance and as well in those with partial tolerance. In contrast, children who were non-responders in the elimination group or those who had to stop SOTI had no significant change in their sIgE levels. Interestingly, non-responders in the SOTI and control groups had the highest sIgE values. Similarly, Meglio et al. (14) deduced from their data that the higher the sIgE levels, the higher the possibility for failure of SOTI.

Efficacy rates for permanent tolerance were the same for SOTI and elimination diet in the present study. However, including patients with partial tolerance in our group revealed similar immunological modifications with a significant reduction in sIgE. From the clinical point of view, these are the children who profit considerably from SOTI as quality of life is increased and the risk for severe allergic reactions in case of accidental ingestion is decreased. In our case series, the overall rate for tolerance was 64% with corresponding immunological changes. In the literature, in a case series of 13 adult patients with food allergy to CM, eight out of 13 patients reached permanent tolerance and the remaining three patients developed partial tolerance with SOTI. The authors speculate that with consequent SOTI for 1.5–2 years, 'real' desensitization is reached as shown by the disappearance of IgE antibodies (21). Patriarca et al. (13) also observed a significant decrease in sIgE levels after 18 months.

A causal treatment of food allergy is particularly important for persistent cases with a high risk of fatal anaphylactic reactions in case of inadvertent ingestion such as peanut allergy. In a case report of Mansfield, a 6-year-old girl with severe peanut allergy in whom the strategy of avoidance and epinephrine autoinjection was not successful, SOTI could induce tolerance up to a maximum dose of four whole kernels three times daily over a period of 8 weeks (27). Tolerance has been maintained by regular daily intake of four whole peanuts along with respective immunological changes. Similarly, in the study by Buchanan et al. (28), seven patients with

HE allergy underwent SOTI with the short-term goal of protecting them against accidental ingestion reactions and the long-term goal of inducing lasting clinical and immunological tolerance. In contrast to the present study, however, only seven children were investigated without a control group. Moreover, the maintenance dose for HE was only 300 mg of powdered HE in contrast to the 2000 mg in the present study. This might be especially important because it is known from subcutaneous immunotherapy that the cumulative dose correlates with the outcome of tolerance development.

Recent case reports concentrated on the method of rush-SOTI. In contrast to the conventional method, doses are doubled and given several times a day (10). The first report was on CM (29), followed by other case reports (30, 31). Further studies are required to evaluate whether rush-SOTI could represent a more efficient strategy to induce tolerance in children with food allergy. Other methods such as sublingual immunotherapy using low-doses or the spit-out method (32, 33) could be further options.

In conclusion, SOTI is an active therapeutic strategy for food allergy if conducted under careful monitoring of an experienced allergic specialist. The threshold dose for allergic reactions is increased considerably, enabling a large number of children to integrate the allergen in their diet. The risk of severe allergic reactions is decreased

substantially in the case of accidental ingestion of small amounts of the offending food. Classification of different patterns to SOTI enables the clinician to determine which patients profit from SOTI best. In some children, regular intake is necessary to maintain tolerance. Augmentation factors that may require intermittent reduction in the dose need to be considered.

Children with low to moderate sIgE levels seem to benefit best whereas patients with high sIgE levels and additional risk factors, such as allergic rhinoconjunctivitis or asthma seem to be the children who are most difficult to treat with SOTI. However, these would be the children who have the greatest benefit because they are most likely to have persistent food allergy. In this way, SOTI is an option especially for patients with persistent food allergy if avoidance cannot be guaranteed, or for those who are eager to eat the food if close supervision of an experienced allergologist is guaranteed.

Acknowledgments

This study was funded by departmental funds. We would like to thank our dieticians Christiane Binder and Mandy Ziegert for diligently performing the oral food challenges, and Gabriele Schulz, Petra Ellensohn and Margret Oberreit for perfect technical assistance in the laboratory.

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