

Review article

Specific oral tolerance induction in food allergy

Specific oral tolerance in food allergy can be induced by oral administration of the offending food, starting with very low dosages, gradually increasing the daily dosage up to an amount equivalent to a usually relevant dose for daily intake, followed up by a daily maintenance dose. Unfortunately, the body of scientific evidence concerning specific oral tolerance induction (SOTI) is still rather poor. Following a couple of case reports, only a few studies on a limited number of patients including different allergens are available. So far, no placebo-controlled, long-term study has been published. Concerning the underlying immunological mechanism, a limited number of studies have reported on changes in antibody production, and more recently on the role of different T-cell populations. The individual pattern of clinical reaction during SOTI seems to vary considerably between patients and from allergen to allergen. Arguments in favour of SOTI are the safety for an inadvertent intake of the offending food and the increased quality of life. Arguments against SOTI are the necessity for a regular intake and possible long-term compliance problems. Indications to consider SOTI in the future might be (i) importance of the incriminated food for the individual nutritional regimen, (ii) avoidance of the corresponding food cannot be assured and (iii) persistent severe food allergy. However, before SOTI can be recommended for the daily praxis, more studies are warranted to clarify whether certain patients may profit from SOTI and to understand the underlying mechanism.

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Food allergy is a common allergic disorder – especially in early childhood. The prevalence of food allergy seems to be increasing (1). Although most patients outgrow their allergy over time, some continue to have clinical reactions over many years. In addition, this tolerance development appears to be allergen dependent with the majority of children allergic to cow's milk or hen's egg become tolerant over time, whereas the majority of peanut allergic patients have persistent allergy until adulthood. Moreover, infrequent consumption of peanuts after tolerance development in peanut allergy may lead to recurrence of the symptoms (2).

The only current treatment options of food allergy are strict allergen avoidance and adequate pharmacotherapy in the event of accidental ingestion. Moreover, treatment with humanized anti-immunoglobulin E (IgE) antibodies protected at least a subset of patients by increasing their threshold dose for allergenic responses (3).

In 1977, first trials were undertaken with subcutaneous injection immunotherapy for food allergy in eight cases. However, patients mainly suffered from non-IgE-mediated

symptoms (4). More recent studies indicate that subcutaneous injection immunotherapy is not recommended for food allergy because of an unacceptably high rate of adverse systemic reactions (5–8). A more recent study investigated the effect of a sublingual immunotherapy (SLIT) with a hazelnut extract in hazelnut food allergy. It was shown that the threshold dose eliciting objective symptoms could be increased after 2 months of SLIT using the spit-out method (9).

In recent years, increasing amounts of the corresponding food allergen have been administered orally, with the aim of achieving tolerance (10–12). This review article provides an overview of the literature on this new therapeutic approach, discusses the advantages and disadvantages, and considers future options.

Principle

In order to achieve tolerance, the offending food is administered orally, starting with very low dosages, which are increased slightly daily up to an amount equivalent to the usual daily oral intake (13, 14). Thereafter, the food is given daily in a maintenance dosage (15).

Abbreviations: DBPCFC, double-blind, placebo-controlled food challenge; SOTI, specific oral tolerance induction.

Nomenclature

As with specific immunotherapy with aeroallergens, which already gave rise to a lively discussion about the correct name (e.g. desensitization, hyposensitization, specific immunotherapy, allergy vaccination), there is no generally agreed term for the administration of steadily increasing oral dosages of the offending food to achieve tolerance in patients with food allergy. So far, oral desensitization or oral hyposensitization has been used (10, 16, 17). We propose the term 'specific oral tolerance induction' (SOTI), because the process (i) seems to be specific (tolerance induction with cow's milk seems not to induce tolerance to hen's egg) and (ii) so far, at least in a subgroup of patients, does not seem to have a long-term effect after termination of its regular intake (15), which could be shown for subcutaneous specific immunotherapy with aeroallergens (18).

Evidence in the literature

Unfortunately, the body of evidence concerning SOTI for food allergy in humans is rather poor. The history started in 1975 with a report on inducing oral tolerance in five cases with the help of 'enzyme potentiation' (19). In 1978, it was observed that feeding a protein to mice might result in both immunization and oral tolerance (20). In the following years, a couple of single case reports have been published in humans. A 12-year-old girl with persistent cow's milk allergy tolerated 200 ml of milk after a 5-day rush protocol (13). One year later, a 6-year-old child with proven cow's milk allergy received increasing amounts of cow's milk over 100 days resulting in a long-term tolerance of dietary foods (21).

In an early open study, 19 individuals (age range 5–55 years) were subjected to oral tolerance induction with one of several allergens (cow's milk, hen's egg, fish and orange), resulting in a success rate of 14 of 15 patients (93%) who correctly followed the regimen (16). In another study, 21 children (mean age 6 years) with severe IgE-mediated cow's milk allergy underwent tolerance induction using a 6-month protocol resulting in a rate of 15/21 children (71%) tolerating the intended dose of 200 ml; three additional children tolerated 40–80 ml (10). A recent study investigating oral tolerance induction in 59 patients (age range 3–55 years) with various allergens using a 60 to 84-day protocol reported a success rate of 83%; 12/59 dropped out because of poor compliance (20%); side-effects such as urticaria, angioedema or abdominal pain were observed in 51% of patients (11). So far, no adequate long-term, placebo-controlled study has been published.

We have reported on three cases in an ongoing SOTI study, which indicate that SOTI can induce oral tolerance in food allergy, but in the absence of daily allergen intake during a secondary elimination phase the tolerance is not necessarily persistent (15).

Mechanism

Oral tolerance is the active nonresponse of the immune system to an antigen administered through the oral route (22). It is postulated that food allergy results from a failure in the establishment and/or maintenance of oral tolerance in infancy (23). However, defective oral tolerance has yet to be demonstrated experimentally in food allergic patients (22).

In general, animal experiments show that two possible mechanisms are the induction of anergy or deletion of responsible cells and the activation of regulatory cells and mediators (24). A study in mice has demonstrated that different feeding regimens after oral tolerance induction with hen's egg white lysozyme induces cell populations that differed in their cytokine secretion profile (e.g. concerning transforming growth factor- β and interleukin-4) and their capacity to actively suppress *in vitro* and to induce anergy (25). Continuous feeding of milk proteins in mice induces suppression of both Thelper 1 (Th1)- and Th2-dependent responses (26). Interleukin-15 does not seem to be involved (27). Epicutaneous exposure to peanut protein prevented oral tolerance and enhanced allergic sensitization in a murine study (28). In other animal studies, the effect of maintenance of oral tolerance could not be attributed to an orally induced antibody formation (29).

Few studies focused on the underlying mechanism of SOTI in humans. In one case report, specific serum IgE decreased and specific serum IgG4 increased over an 18-month observation period (21). In the study of Patriarca, specific IgE decreased significantly after 6 months and specific IgG4 increased significantly after 18 months (11). Nevertheless, these changes in antibody production might be an epiphenomenon, not reflecting the underlying mechanism. The precise immunological basis for oral tolerance induction in humans is by no means clear (30). Future studies on the clinical effects in humans should include experiments elucidating the mechanism of SOTI.

Different patterns of reaction during SOTI

It appears that individual reaction patterns during SOTI differ considerably from patient to patient. As far as can be derived from the literature, there are the following patterns: (i) Life-long tolerance after SOTI appears to be the most common response (10, 11, 16). However, because of a lack of placebo controls in all studies this pattern may reflect either the natural course of the disease over time or may be the result of immune modulation by SOTI. (ii) In a lower percentage of patients the food is tolerated, but only at a lower dosage than the planned full maintenance dosage (10, 11, 16). Further increase leads to clinical symptoms; however, this is a partly positive response, as the safety margin is enhanced. (iii) The food

is initially tolerated with SOTI in the full maintenance dosage, but allergic symptoms re-occur after a period of avoidance (15). This indicates short-term oral tolerance, but not a long-term specific immune modulation in some patients. (iv) In a few patients, the titration steps of the SOTI protocol are never tolerated and the therapy has to be discontinued (SOTI nonresponder) (10, 11).

Pros and Cons

From today’s perspective, a successful therapy with SOTI has the advantage that the patient is protected against reactions through inadvertent intake of small amounts of the offending food. Therefore, the quality of life is increased and the patient is able to eat safely, including processed foods. However, a regular intake does seem necessary. But the patient may not eat the food on a daily basis, or compliance may decline with time. Furthermore, the safety advantage may be low, if the patient is kept constantly close to the clinical symptom threshold dosage with regularly occurring clinical symptoms; or the patients may feel too safe and lose their feeling for risky situations.

Possible indications

If SOTI keeps it promises, indications to consider this therapy in the future may be that avoidance of the corresponding food cannot be assured that the patient is eager to eat foods, which are favourites, but so far not tolerated, or that the incriminated food is an important component of the individual diet.

Open questions

As there is only a very limited body of evidence on SOTI so far, many questions are still open.

Mechanism

- Is there a difference between the primary oral tolerance (e.g. to cow’s milk in nonallergic patients) (31) and the tolerance induced by SOTI in food allergic individuals?

- Does SOTI ‘only’ increase the threshold dose necessary to elicit allergic symptoms or does it mimic tolerance development during the natural course of the disease?
- Does SOTI have a transient or a permanent effect?
- Is a life-long daily exposure necessary to maintain oral tolerance?
- If so, which is the minimum dose and minimum time interval between single doses (days or weeks) necessary to maintain the oral tolerance?
- Can immunological changes be proved, e.g. in blood after successful SOTI?
- Is successful SOTI restricted to IgE-mediated clinical symptoms?
- Is the success rate of SOTI allergen-related (e.g. better for cow’s milk than peanut)? If so, are highly allergenic foods such as peanut not suitable for SOTI, because of safety considerations?

Methods

- What is the optimum individual starting dose? Is the proposed starting dose referring to skin prick test endpoint titration meaningful, as recently proposed (12) or can it be related to the threshold of clinical reaction during the oral food challenge of the corresponding food?
- Which titration procedure results in the best compromise between the shortest possible time period and the best efficacy and/or safety? (Table 1)
- Which is the optimum maintenance dose? High doses compared with the preferred daily intake or lower doses sufficient to protect patients from accidental intake; is the lower dose sufficient to induce tolerance over time.

Trials

- Which is the best way to study SOTI in clinical trials? Double-blind, placebo-controlled trials would be desirable, but blinding may be difficult to guarantee, if highly sensitized/allergic patients notice clinical symptoms, or their absence with the placebo. Furthermore, it may be unethical to leave patients uncertain about whether oral tolerance has been achieved or not.

Table 1. Comparison of a usual oral food challenge regimen with two different hypothetical specific oral tolerance induction (SOTI)-protocols

Parameter	Titrated oral food challenge (32)	SOTI conventional procedure (15)	SOTI rush procedure (13)
Starting dose of protein	Low	Very low	Very low
Time between steps	Usually every 30 min	Every 24 h	Approximately every 2 h
Number of steps	Several (e.g. 5–10)	Many (e.g. 40–60)	Many (e.g. 20–40)
Increment of steps	Half-logarithmic	Less than doubling doses	Doubling doses
Time for whole procedure	Usually 4–5 h	Minimum 2–3 months	Approximately 1 week
Maximum dosage (approximate)	3–5 g protein	3–5 g protein	3–5 g protein

Conclusions

Specific oral tolerance induction seems to represent an interesting and promising approach for the therapy of food allergy improving the quality of life and the safety in

the event of accidental intake of the offending food. However, there have not yet been any placebo-controlled studies investigating the long-term effects. Further studies are warranted to assess how patients may profit from SOTI and to understand the underlying mechanism.

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