

Novel Approaches in Treating Food Allergy Using Allergens

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Abstract

Food allergy may be life-threatening and its management continues to consist of avoiding relevant allergens and, in the case of accidental ingestion, initiation of appropriate emergency therapy. The purpose of this review is to highlight the most promising novel approaches for treating food allergy using allergens. The use of specific immunotherapy for food allergy treatment is described. Clinical trials of immunotherapy have been published in the past. However, randomized, placebo-controlled studies are needed, including the evaluation of immune mechanisms. Immunotherapy is mainly indicated for persistent food allergy after the usual age of recovery. Reactive dose and symptoms of food allergy are less defined to indicate immunotherapy. Several procedures have been described: subcutaneous with constant adverse effects; oral tolerance induction with efficacy in a third of the cases, and sublingual which seems promising. The significance of the immunotherapy effect, persistent or transitory, or increasing the tolerated dose need to be defined.

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Up to 6% of young children and 2% of adults suffer from food allergy [1, 2]. The necessity of a strict avoidance diet, its implementation in the community such as daycare or school, and the constant potential risk of an anaphylactic reaction after accidental ingestion of the offending food have a major impact on the quality of life of affected patients and their families [3]. Here we review the recent developments in novel approaches to treating food allergy using allergens.

Various options for the treatment of food allergy have been explored using allergens. These methods are being developed primarily for use in the treatment of respiratory allergies; potentially some may be applied to the treatment of food allergies.

The characteristics of the immune response in patients with IgE-mediated food allergy have partially been elucidated. Allergic individuals have Th2 skewing of their immune response leading to IgE production after exposure to potentially allergenic foods. Studies in animal models of allergy suggest that tolerance involves regulatory T cells and the secretion of specific cytokines in particular IL-10 and TGF- β [4]. These findings suggest that effective immunotherapy can be assessed by an antigen-specific immune response skewed towards the expression of T-regulatory cells.

Immunotherapy Protocols

Recent studies on the use of immunotherapy with food include the diagnostic workup of food allergy based on oral food challenge. Nevertheless, few studies have been carried as double-blind, placebo-controlled food challenge (DBPCFC) tests with control groups, which makes the conclusions dubious.

Several Protocols

Various protocols have been published. The fastest includes the ingestion of increasing amounts of initially diluted food which is repeated during the day so that the required amount is usually consumed within in a few days. Other slower protocols begin with a diluted or undiluted food, slowly increasing the quantity so that the complete amount is achieved within a few months [5–7].

Efficiency

Optimistic results have been reported for various foods such as cow's milk, hen egg, fish, and also orange, apple, beans, peach, and wheat [5, 6]. The results are often very positive, with an almost 100% cure for some [5]. Nevertheless, studies with control groups reveal much more mitigated results with 36% cure [8]. Moreover, if tolerance is acquired, regular ingestion of the food is necessary to maintain it [9].

Adverse Effects

Allergic reactions reported during protocols of immunotherapy are varied: flare-ups of eczema, urticaria, edema, abdominal pains, rhinoconjunctivitis, or asthma [5–8].

Immunotherapy Procedures

Several procedures have been published using subcutaneous, oral, or sublingual methods.

Subcutaneous Immunotherapy

The severity of the reaction in peanut-allergic patients led investigators in the early 1990s to start a rush immunotherapy trial with crude, unmodified peanut extracts in patients with severe symptoms [10, 11]. Measures of efficacy included a symptom score with DBPCFC and titrated skin prick test results. In the first study, in the 3 subjects who completed the peanut immunotherapy studies, a 67–100% decrease in symptoms was measured during the DBPCFC test. However, the rate of systemic reactions with rush immunotherapy was 13.3%, but unfortunately 1 patient died after immunotherapy injection [10]. The following study included 12 patients with marked sensitivity to peanuts [11]. Half underwent immunotherapy with aqueous peanut extracts over 1 year. Upon DBPCFC test all treated patients experienced increased tolerance to peanut. However, systemic reactions were common in this group of patients and half of them required dose reduction. After dose reduction, partial tolerance to peanuts was partly or completely lost on oral challenge. These two trials were mostly hampered by severe allergic reactions after allergen injection, and they cannot be considered as safe treatment options for food allergy. From these studies, it can be concluded that subcutaneous immunotherapy with peanut extract carries a high risk of severe side effects and that they are only partially effective.

Specific Oral Tolerance Induction

Antigen exposure in the gut leads to protective local and systemic immunologic responses. Frossard et al. [4] demonstrated the potency of oral tolerance induction (OTI) when mice were fed high-dose β -lactoglobulin. Oral tolerance to β -lactoglobulin was associated with diminished T-cell proliferation in both spleen cells and mesenteric lymph node cells after stimulation with β -lactoglobulin.

OTI to foods has been reported in numerous limited series with varying results [5, 8] (table 1). It can be stated that while many patients were reporting to tolerate increasing amounts of foods, most were still reactive to larger quantities. Furthermore, the effectiveness of the procedure relies mostly on the daily ingestion of a certain amount to keep the partial tolerance achieved by this procedure.

Meglio et al. [6] studied the effects of specific OTI (SOTI) in 21 children (>6 years old) allergic to cow's milk. Using a very slow protocol, the percentage of cure from the cow's milk allergy was 71.4% at 6 months with a tolerated quantity of milk of at least 200 ml. Moreover, 14.3% of the children tolerated quantities of between 40 and 80 ml cow's milk/day, and 14.3% of the children failed.

The study by Buchanan et al. [12] was carried out on 7 patients allergic to egg. All the patients were improved after 24 months of SOTI, 4 patients were considered cured, and 3 others tolerated a limited quantity of egg between 2 and 14.7 g. Nevertheless, the results of another study including 21 patients

Table 1. Selected randomized SLIT and OIT studies with control group (n =19)

	Allergen received (number of subjects)	Length of therapy	Efficacy
<i>Sublingual</i>			
Enrique et al. [16], 2005	Hazelnut (11)	8–12 weeks	5 (45%) of 11 reached highest dose (20 g) in food challenge
<i>Oral</i>			
Patriarca et al. [5], 2003	Cow's milk (24)	18 months	Desensitization was successful in 45 (77%) of 58 treatments
	Whole egg (13) Albumin (3) Fish (10) Orange (2) Peanut (1) Corn (1) Peach (1) Apple (1) Lettuce (1) Beans (1)		
Meglio et al. [6], 2004	Cow's milk (21)	6 months	15 (71%) of 21 achieved daily intake of 200 ml; 3 tolerated 40–80 ml/day
Buchanan et al. [12], 2007	Egg (7)	24 months	4 (57%) of 7 passed food challenge with 8 g of egg at conclusion of therapy; 2 passed second challenge 3–4 months later
Staden et al. [8], 2007	Cow's milk or egg (45)	11–59 months	9 (36%) of 25 who received allergen achieved permanent tolerance; 7 (35%) of 20 who underwent elimination diet achieved permanent tolerance
Longo et al. [14], 2008	Cow's milk (30)	12 months	11 (36%) of 30 achieved daily intake of 150 ml/day; 16 (54%) of 30 tolerated 5–150 ml/day

were less favorable [13]. The side effects described were pruritus, urticaria and abdominal pains [13]. The SOTI failed in 2 cases [13].

Patriarca et al. [7] published a series of 59 patients with food allergy who underwent OTI. The population consisted of a mixed sample of adults and children. Twenty-nine were allergic to milk, 18 to egg, 11 to fish, and 9 to other foods. The diagnosis relied on skin prick tests and/or assessment of serum-specific IgE levels. DBPCFC procedures were also used in some patients. SOTI for the different foods was then applied to all subjects. The inductions were stretched over 60–84 days up to a maintenance dose of 120 ml milk, 50 ml egg or 160 mg boiled codfish. The authors reported the success of OTI in 24 of 29 patients with milk allergy, 13 of 15 patients with egg allergy, and 8 of 11 patients with fish allergy. However, the authors reported that OTI could not be completed in some patients because of recurrent urticaria or gastrointestinal symptoms. Unfortunately, this study was not validated by a control group and was not blinded.

One of the most recent studies concerning oral tolerance using a control group was performed by Staden et al. [8]. SOTI was compared with a strict avoidance diet. Cow's milk and hen egg were the 2 foods tested. The results were expressed in 4 clinical profiles. The responders (36% of the cases) tolerated the food completely and were regarded as cured. Twelve percent of the responders tolerated the food only if it was consumed regularly and lost tolerance by avoidance. The partial responders (16%) tolerated limited quantities of food, and 36% of the children were non-responders. The results are comparable with the group on a strict avoidance diet as in this group 35% of the children were regarded as tolerant. The lowered IgE specificity is more increased in tolerant children than in those on SOTI or diet, with a significant difference ($p < 0.001$) between the tolerant subjects and partial responders – non-tolerant. Among the side effects observed, a flare-up of eczema was more frequent in the SOTI group than in the group on the diet. General cardiovascular symptoms were only increased in the diet group. Ultimately, if SOTI does not seem more effective than a traditional avoidance diet, it at least has the advantage of allowing a progressive increase in the amounts of food by reducing the risks of a severe reaction.

A controlled study of oral tolerance therapy in children with severe allergy to cow's milk found significant differences between those who underwent therapy and those who followed an elimination diet [14]. Sixty children, aged 5 years or older, with a history of severe allergic reactions and very high levels of IgE specific to cow's milk protein were divided into 2 groups. One group underwent SOTI to cow's milk, and the other was kept on a milk-free diet. After 1 year, 36% of children in the treatment group tolerated milk (at least 150 ml daily) completely, 54% were able to tolerate 5–150 ml milk daily, and 10% did not complete the protocol due to persistent respiratory or abdominal complaints. Tolerance was confirmed in an open feeding observed by the investigators. In contrast, in the group that maintained an elimination diet, all

30 patients failed a DBPCFC after 1 year. Half the patients in the treatment group had significant decreases in IgE levels specific to cow's milk at 6 and 12 months. In the control group, milk-specific IgE levels remained essentially unchanged, and none of the children acquired tolerance spontaneously.

Preliminary results show that tolerance to milk and egg can be induced in some patients with persistent food allergy [5, 8, 12]. Well-designed placebo-controlled studies are needed for proper assessment of the method. However, symptoms of food allergy may resume when treatment is discontinued [9].

Sublingual Immunotherapy

The immune mechanisms of sublingual immunotherapy (SLIT) take into account the role of regulatory T cells producing IL-10 and oral mucosa Langerhans cells expressing high-affinity IgE receptors in inducing allergen tolerance [15].

SLIT has been successfully used in one trial to treat patients with hazelnut allergy [16]. Twenty-three adults allergic to hazelnut were randomized to receive a standardized hazelnut extract or placebo using a sublingual-spit rush protocol over 4 days. They then received maintenance SLIT for almost 3 months. Systemic reactions were rare and responded to antihistamine treatment. On repeat DBPCFC, the mean quantity of hazelnut provoking objective symptoms in the active treatment group increased from 2.29 to 11.56 g ($p = 0.02$), while the placebo group had only a nonsignificant increase from 3.49 to 4.14 g. Moreover, almost 50% of patients who underwent hazelnut SLIT tolerated the highest dose of 20 g. The increase in hazelnut tolerance in the treated group was accompanied by increases in serum hazelnut-specific IgG4 and IL-10. From these methodological and immunological data taken together, it seems that SLIT for food allergy could be a useful tool for understanding the immune mechanisms underlying food tolerance, and the role of dendritic cells and regulatory T cells in this process.

Other studies dealing with SLIT as a safe and efficacious treatment for food allergy, and studies on long-term efficacy are required.

Other Treatments using Modified Foods Allergens

Mutated allergen protein immunotherapy or peptide immunotherapy are currently being evaluated in a mouse model of peanut allergy. The potentially severe side effects of immunotherapy could be controlled using modified or peptide allergens [17, 18]. More extensive immunotherapy protocols are being investigated.

Conclusion

IgE-mediated food allergy is a common disease with potentially severe or fatal reactions in some patients. The lives of these patients are mostly

impaired by a strict avoidance diet and the risk of accidental ingestion due to contamination of processed foods. Efficient proactive treatment of food allergies is needed for these patients. Nevertheless, promising new therapeutic modalities for food allergy with high safety and efficacy are being developed. Immunotherapy could represent a new approach in the treatment of food allergies [19]. The natural history of the food allergy must be taken into account. The methods remain dubious, and randomized, placebo-controlled studies are needed, including evaluation of immune mechanisms over time. It is not yet possible to establish whether the effects of immunotherapy correspond to a final cure or only an increase in the allergen level thresholds.

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Discussion

Dr. Isolaure: There was an early publication from France on early treatment approaches to cow's milk allergy and egg allergy [1]. Do you have a long-term follow-up of this cohort and how long does this effect last?

Dr. Rancé: The study performed by Morisset et al. [1] was performed for prevention and not to achieve tolerance. This study is ongoing and there is no recent publication.

Dr. Heine: The natural history of food allergy is quite variable. For example, in cow's milk and egg allergy tolerance often develops in the first years of life. Immunotherapy should therefore be compared against natural tolerance development. I wonder whether any patients who developed tolerance in these trials would have developed tolerance anyway. Has anyone looked at older patients with high specific IgE levels who would not be expected to develop tolerance?

Dr. Rancé: You are right. With a high quantity of food, we don't know if it is a persistent tolerance or not. Studies looking at immune response are missing.

Dr. Conway: For years we have been using lactobacillus and probiotics to function as a vaccine, as adjuvants together with vaccines such as salmonella or cholera toxin. Looking at the fact you are getting some responders and some non-responders and you are looking at strict control of the diet in terms of the specific allergens, are you also looking at control of the diet in terms of potential adjuvants that could be interfering or in fact enhancing the induced tolerance?

Dr. Rancé: Yes, it could be an adjuvant. But looking at the last study, there was nothing in the dietary group, there was no modification on the specific IgG or IgE in the threshold levels of food challenge. According to the natural history of food allergy, some children could be improved in this group.

Dr. Conway: So when you do dietary control, you are simply observing the intake of the allergen and not all the potential immune-triggering components?

Dr. Rancé: There was nothing with regard to the immune-triggering components.

Dr. Prescott: With regard to predictive markers, who might be the non-responders, the responders, or these people who are dependent on regular allergen exposure? What is the optimal age to do this? Particularly with foods where the natural history is not to outgrow them, for example peanuts, nuts, etc., perhaps if we do specific oral tolerance induction earlier it may be more successful. I don't know the answer to that at all, but I wonder what you think.

Dr. Rancé: We don't know today because there are very few studies on this aspect. It is not easy to include children with very severe allergy. Specific oral tolerance induction can be dangerous, and some use epinephrine. We don't have an answer with regard to age.

Dr. Prescott: The risk of death is less in younger children though, so there may be cost benefits there.

Dr. Wiedermann: You mentioned briefly that a child doesn't grow out of allergy easily if the allergen is linear and not a confirmational allergen. What is known about the role of T-cell responses in these allergic children. Is it that there are perhaps more T-cell epitopes in linear allergens which could play a role in the perpetuation of the allergic responses?

Dr. Rancé: I cannot answer that. Perhaps someone here can answer. But if you can predict which children will have more persistent allergy, this would be very interesting.

Dr. Wen Chin: I am interested in the study that you are doing on sublingual immunotherapy for cow's milk. Is there a difference in the preparation or the dosing of sublingual immunotherapy for cow's milk versus oral immunotherapy for cow's milk?

Dr. Rancé: For sublingual immunotherapy with milk, we start at 0.1 ml and increase the dose up to 0.8 ml. This dose is retained every day for 6 months, followed by an oral food challenge. With oral immunotherapy, the doses were increased every week to reach large amounts.

Dr. Wen Chin: So it is almost oral immunotherapy for cow's milk; it is just a diluted preparation.

Dr. Stanley: My comment is that I would like to see so-called food allergy subdivided. I think a lot of children with different conditions have been lumped together. For example, if you put milk on the skin of children with eczema, they will develop an urticarial eruption. Small children don't know where their mouths are and when they drink milk they it spread all over their mouths and get urticarial eruption as an angiodema on their mouths. I don't believe these children have the same condition as children who swallow their food and develop a systemic reaction or a gut reaction, but they have all been put together into one group, and I think we should actually be subdividing children when we report on food allergy. That's just an observation. My question is related to kiwi fruit. I see a huge number of children with allergies in New Zealand, and although kiwi fruit is readily available, kiwi fruit allergy is very uncommon. In Europe everyone is talking about kiwi fruit allergy; so there are two possibilities that I think need to be reviewed here. One is the process of shipping kiwi fruit in which gases are used to prevent the kiwi fruit from ripening; those gases may alter the allergenicity of kiwi fruit. The other possibility is that the kiwi fruit produced in Europe may in some way be different. When people report kiwi fruit allergy, it would be helpful to know what sort of kiwi fruit it was and where it came from.

Dr. Rancé: Thank you for your comments. You are right because we have to look at age. Firstly that is the natural history, this protocol is more for children with persistent allergy and not with very young children. Secondly, with regard to kiwi fruit, Lucas et al. [2] looked at the allergen and found no differences according to the species of kiwi fruit. In Europe we eat a lot of kiwi fruit because it is an inexpensive source of vitamin C.

Dr. Salminen: How to assess allergens is also a key question for the food safety authorities in Europe. We have gone a little bit off the main topic, but if the mechanism can be found and the differences between New Zealand and Europe identified, it will certainly have an impact on the food safety issue.

Dr. Heine: Just a question regarding egg allergy. We know that cooking alters the antigenicity of egg. There is debate whether we should recommend strict egg avoidance or whether egg-allergic patients can continue to have cooked egg in their diet, if they tolerated. What is your practice in France?

Dr. Rancé: Practice is the same in France, and it is the same with milk. Some children tolerate boiled milk but not crude milk. For this protocol it is difficult to use this modification with cooking. Our patients are told that if they tolerate cooked egg, they should only eat cooked egg but not raw egg.

Dr. Fox: I think this very much relates to a recent paper by Nowak-Węgrzyn et al. [3] who proposed two different phenotypes of milk allergy. One type relates to children with IgE directed at linear epitopes (who tend to have more persistent milk allergy and more severe reactions) and the other phenotype who have IgE predominantly directed at conformational epitopes (who tend to have more transient milk allergy and tolerate extensively heated milk). Do you not suspect that in these different studies, the children who are not responding are the ones who have IgE against linear epitopes and thus grow out of their allergy anyway, whilst the ones who seem to develop tolerance are the ones who have the milder phenotype. If so, then whilst the epitope-binding pattern may help us predict the response, the only children being helped are actually the ones who need help the least!

Dr. Rancé: I agree totally with that, but do you think it is possible to look at the epitope? Today it is not easy, and secondly it is not reproducible for all the children, that is the problem.

Dr. Isolauri: I would like to come back to dietary compounds modifying the antigens. In the first preclinical studies we made with *Lactobacillus rhamnosus* GG, we found a significant suppressive effect with casein compounds degraded by enzymes of this lactobacillus compared to casein degraded by pepsin and trypsin. Secondly there is the question about food challenge protocols. The patient should ingest the protein, so if food challenge is stopped on seeing a reaction on skin application that of course needs to be reported. Finally a comment on kiwi fruit. Kiwi fruit allergy is common in Scandinavia and Europe, and the most positive skin prick test reactions are to mango and kiwi fruit. This is because we used to advise children to start solid foods with mango, kiwi fruit and that sort of imported foods, and not the common foods we have in Finland.

Dr. Swain: In Australia over the last 5–10 years, we have also observed an increase in kiwi fruit allergy and we wonder whether it is related to the increased consumption and also the varieties that we are seeing. Similar to in Finland, we have a trend to use kiwi fruit as a healthy takeaway portable food for infants: you just cut it in half, scoop it out with a spoon, and give it to the children. So we have seen more kiwi fruit allergy developing in Australia. We have also seen a number of adults developing kiwi fruit allergy over the last 10 years. So our experience seems to be similar to yours.

Dr. Rancé: In adults it is different because it is a cross-reaction between pollens and fruits or legumes, so it is not the same mechanism in adults.

Dr. Swain: No, but in children we definitely see a major increase in kiwi fruit allergy.

Dr. Du Toit: The problem with all the studies is study design. We are all trying to figure out or differentiate the process of tachyphylaxis from natural history or true desensitization or tolerance induction. You have a lot of experience in this. How ideally do you see the study design? Obviously we need a control arm. The problem with the control arm, as I understand it and we found this in the LEEP studies, is you need to challenge the children at the beginning of the study to determine a threshold dose but the challenge in the control arm is a form of therapy in itself. So you already start off with an initial dose and then at the end of the study you can challenge the children. In your active group that is taking milk or egg or whichever food, do you suggest that there is an interval where they don't ingest it and then you re-challenge them? Because of the previous paper we are obviously all concerned that you may induce anaphylaxis after a period of avoidance. So my question is how do you see the ideal study design?

Dr. Rancé: You are right, we have to make the protocol uniform because in the study by Staden et al. [4] challenge was performed after 2 months of avoidance and that was able to stop tolerance. So we need more studies performed without a period of avoidance.

Dr. Brandtzaeg: A quick question for my own clarification. In our experience almost half of the children with cow's milk allergy do not have a detectable IgE response, so we call them non-IgE-mediated allergy. To my knowledge such cases were excluded from all these sensitization studies you are referring to.

Dr. Rancé: Yes, they were excluded.

Dr. Brandtzaeg: Because we found in those with no IgE response that when they grew out of their allergy, they actually developed regulatory T cells, which is really a mechanism to consider [5]. Are there no studies on immunotherapy of those who are non-IgE-mediated?

Dr. Rancé: Most of these protocols are for IgE-mediated food allergy.

Dr. Brandtzaeg: Yes, but I presume they distinguish the groups in the studies.

Dr. Rancé: I don't know of any study performed in non-IgE-mediated allergy, but first we have to know about the immune mechanism and immune response. That is not done today and it is really needed.

Dr. Brandtzaeg: We know that those who grow out of their non-IgE-mediated cow's milk allergy actually develop or expand regulatory T cells [5].

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