Immunotherapy in food allergy: towards new strategies

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Summary

Allergen avoidance is the standard treatment for managing food allergies. Complete avoidance is difficult, and accidental exposure often occurs. Immunotherapy is a significant focus for treating food allergies, and oral immunotherapy (OIT) appears to be particularly effective in inducing desensitization. The majority of patients who receive OIT show increased threshold doses of their food allergen. The efficacy of OIT is different among food antigen, and milk OIT is relatively difficult to achieve tolerance. OIT may induce mild to moderate symptoms during the therapy, widespread acceptance of OIT for long-term therapy is unclear. Recently, novel immunotherapies for food allergies, such as sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) and using an anti-IgE monoclonal antibody (omalizumab), have been assessed. In addition, a combination of OIT with omalizumab, which was found to increase the threshold doses of the offending foods without producing adverse reactions, may be effective and useful in the treatment of food allergies. These treatments have been used only in research settings; further studies in large numbers of patients are needed to demonstrate their long-term safety and benefits in clinical practice. ***(Asian Pac J Allergy Immunol 2014;32:195-202)***

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Introduction

Food allergies have become ever more prevalent in recent decades. The current management for food allergy includes identifying the offending foods and avoiding them.[1] Because accidental exposure to food allergens often occurs,[2] patients must be prepared to treat an allergic reaction. The difficulty in avoiding the foods to which they are allergic and the potential for an unexpected sudden and life-threatening reaction[3] diminish the quality of life both for the patient and his family.

The concept of immunotherapy is not new, but it has not been practical. Subcutaneous immunotherapy (SCIT) for peanut allergy was rejected owing to the high rate of severe adverse reactions.[4] Recently, oral immunotherapy (OIT) has been investigated as a therapeutic approach for food allergy,[5-12] and numerous clinical trials, including randomized controlled trials, have been completed. More recently, sublingual immunotherapy (SLIT) and epicutaneous immunotherapy (EPIT) with an anti-IgE monoclonal antibody (omalizumab) have been examined. These treatments increased patient threshold doses of food and decreased the incidence of adverse reactions, and they may be useful to treat food allergies. In this paper, we review the clinical trials of OIT as well as recent advances in other immunotherapies for managing food allergies.

Oral immunotherapy

Immunologic responses with OIT

Although the mechanism of OIT has not yet been clearly demonstrated, it has been shown to induce desensitization and tolerance (Figure 1),[13] compared to baseline values, at 12 and 18 months (Figure 2).[7] Antigen-specific IgE levels in subjects receiving OIT tended to increase early, but decreased subsequently. A significant increase in specific IgG levels occurred after the patients had been on OIT for 3 months, but the levels gradually returned to baseline by 33 months. On the other hand, specific IgG4 levels increased initially and remained elevated until the end of the study. OIT is most commonly associated with a reduction in antigen-

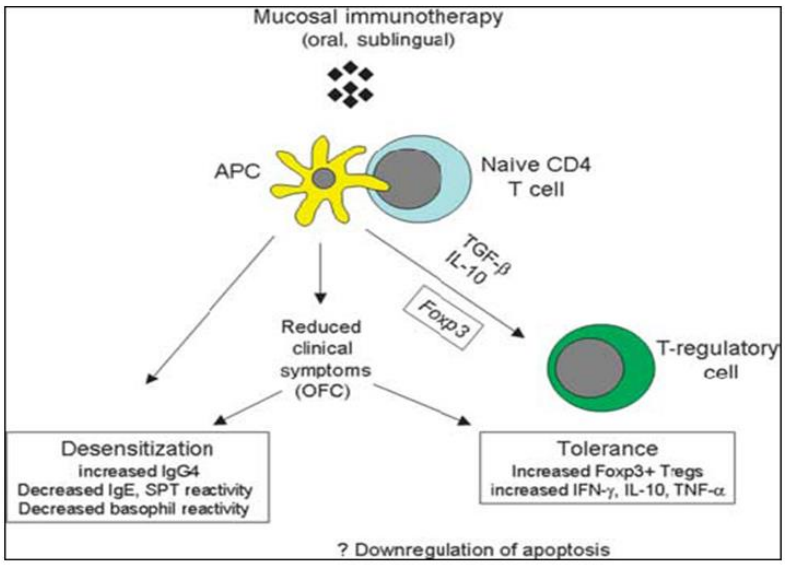

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Figure 1. OIT induces both desensitization and tolerance

specific IgE level and an increase in antigen-specific IgG4 level, although some studies have reported no change in antigen-specific IgE levels during treatment with OIT.[5,6,14,15] Since these changes in antigen-specific IgE, IgG, and IgG4 levels were seen only in subjects receiving OIT, these immunologic responses seem to be allergen-specific.[16] More recently, Vickery et al reported that these immunologic responses were associated with changes in epitope binding patterns, indicating that OIT induces shifts in the antibody repertoire.[17]

Modulation of immunologic cells is thought to be a predominant mechanism for immunotherapy (Figure 1).[13] Skin prick test (SPT) reactivity showed a significant decrease several months after a course of treatment and it remained diminished throughout the three-year follow-up.[7] Additionally, some early studies reported that OIT induced a reduction in basophil count, which was evident four to six months after treatment.[7,18] Burks et al. also reported that basophil activation decreased with OIT administration and that the reduced basophil activation was associated with desensitization.[15] Moreover, OIT reduced Th2 and increased regulatory T cells (Treg) counts. Blumchen et al. reported that peanut OIT was associated with reduced peanut-induced Th2 cytokine production (IL-4 and IL-5).[9] In contrast, Jones et al. reported increased IL-5 and TNF-α production in patients who underwent peanut OIT.[7]

Efficacy of OIT

Many studies have shown that the majority of subjects receiving OIT were desensitized and that continuous allergen exposure increased the threshold of clinical reactivity to food[5,6,9,11,12,15] (Table 1). On the other hand, whether or not the tolerance induced by OIT resembles natural tolerance that has spontaneously developed in food allergy patients is unknown.

Several controlled studies of patients with peanut, milk, and egg allergies have shown that OIT increases the threshold of reactivity to the causative food. Varshney et al. reported a study of peanut OIT in 28 subjects with peanut allergy.[19] After therapy, 16 (93%) of the 19 subjects who received active treatment were able to ingest 4.0 gram of peanut protein, whereas the control subjects reacted to doses less than 0.28 gram. In 2014, Anagnostou et al. reported the results of a phase 2 randomized controlled trial of peanut OIT,[20] which showed that OIT induced desensitization in most subjects with a peanut allergy of any severity, a clinically meaningful increase in the peanut threshold.

Equal numbers of milk OIT trials and peanut OIT trials have been published. Table 1 shows the results of just the randomized controlled trials.

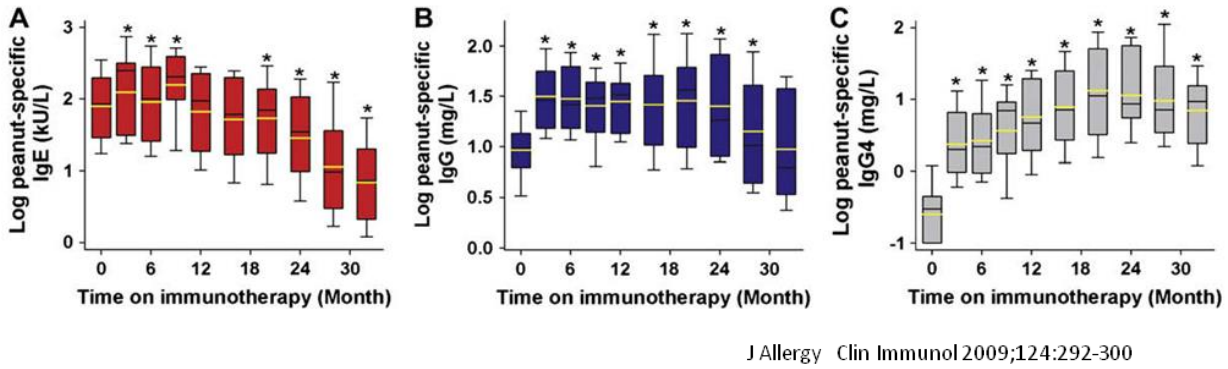

Figure 2. Changes of peanut-specific Immunoglobulins levels during peanut OIT

Table 1. Efficacy of OIT for food

Food	Study (published year)	Subjects	Duration/ Target dose	Clinical outcomes 1	Clinical outcomes 2
Peanut	Varshney et al. (2011)	2-10 years OIT: 19 Control: 9	Duration of OIT: 48 weeks Target dose: 4000 mg	OIT: threshold dose ↑ Control: threshold dose was lower than OIT group	Desensitization: 84% Dropout: 16%
	Anagnostou et al. (2014)	7-16 years OIT: 39 Control: 46	Duration of OIT: 24 weeks Target dose: 800 mg	OIT: threshold dose ↑ Control: no changed	Desensitization: 62% Dropout: 2%
Milk	Longo et al. (2008)	5-17 years OIT: 30 Control: 30	Duration of OIT: 1 year Target dose: 150 mL	OIT: threshold dose ↑ Control: no changed	Desensitization: 36% Dropout: 10%
	Skripak et al. (2008)	6-17 years OIT: 13 Control: 7	Duration of OIT: 13 weeks Target dose: 15 mL	OIT: threshold dose ↑ Control: no changed	Desensitization: 46% Dropout: 8%
	Pajno et al. (2010)	4-13 years OIT: 15 Control: 15	Duration of OIT: 48 weeks Target dose: 200 mL	OIT: threshold dose ↑ Control: no changed	Desensitization: 67% Dropout: 10%
Egg	Burks et al. (2012)	5-11 years OIT: 40 Control: 15	Duration of OIT: 22 months Target dose: 2000 mg	OIT: threshold dose ↑ Control: no changed	Desensitization: 55% Tolerance: 28% Dropout: 13%

These studies found significant differences between patients who underwent OIT and those who maintained an elimination diet.[5,11,14] The success rate for desensitization ranged from 36 to 67%. The lowest rate reported was in a study in which severely milk-allergic subjects with a history of anaphylaxis to milk and milk-specific IgE levels above 85 kUA/L were enrolled.[11]

Fewer egg OIT trials than peanut or milk OIT trials have been described. In 2012, Burks et al. reported a double-blind, randomized, placebo-controlled study of egg OIT in 55 children with egg allergy.[15] After 10 months of therapy, not one of the children who received a placebo and 55% of those who received OIT passed an oral food challenge (OFC) and were thus considered to be desensitized.

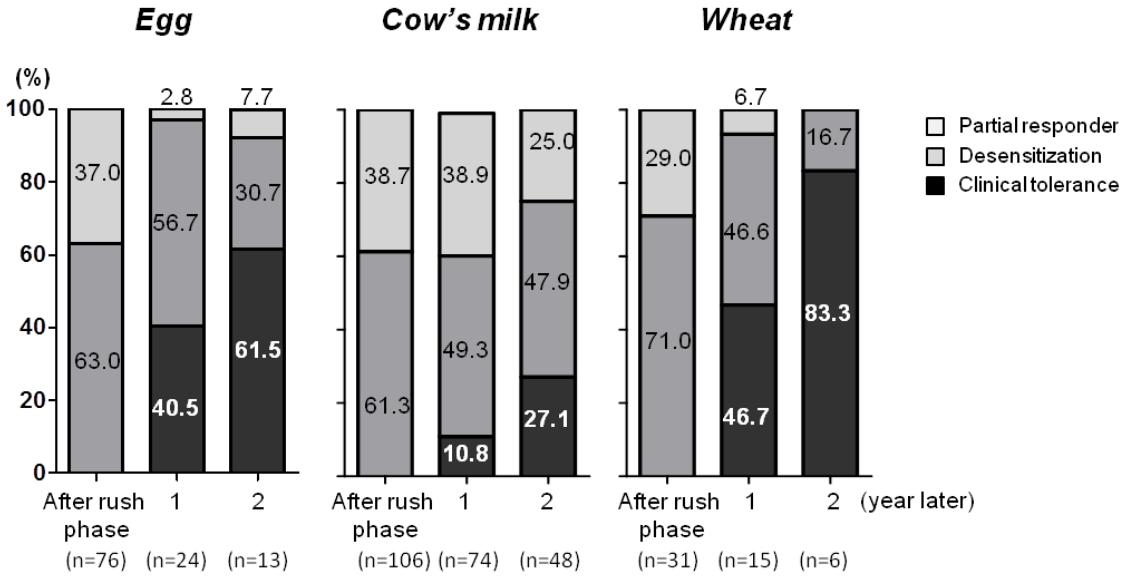

Figure 3. Efficacy of OIT measured at 2 year follow-up

Twenty-two months after the therapy began, 75% of children in the OIT group had been desensitized. Furthermore, after two months of complete egg avoidance, 28% (11 of 40 children) of the OIT group passed the OFC at 24 months, and their unresponsiveness to the allergen was considered to be sustained. At 30 months and 36 months, all children who had passed the OFC at 24 months were consuming egg without any problem.[15]

These studies mostly excluded patients with food-induced anaphylaxis. Since 2008, in National Sagamihara Hospital, we have been using OIT in patients with egg, cow's milk, and wheat anaphylaxis.[21] We have enrolled over 250 patients with food anaphylaxis, defined by a double-blind, placebo-controlled, food challenge (DBPCFC). Our OIT protocol consists of three steps: 1) initial build-up phase in the hospital, 2) slow build-up phase at home, and 3) maintenance phase. Finally, while the patients were on the maintenance dose for 3 months or more, they discontinued OIT for 2 weeks and returned for a final OFC, to determine their tolerance for the offending food. After two years, 92.2% of patients on egg OIT (daily intake of 1 heated whole egg), 75.0% of the milk OIT patients (daily intake of 200 mL milk), and 100% of wheat OIT patients (daily intake of 5.2 g of wheat powder) had been successfully desensitized (Figure 3). Moreover, the patients who had passed OFC at the end of the therapy included 61.5% of those on egg OIT, 27.1% of those on milk OIT, and 83.3% of those on wheat OIT; these patients might achieve clinical tolerance. The efficacy of OIT seems to differ among food antigens, in cases of severe food allergy. It is comparatively difficult to achieve clinical tolerance with milk OIT.

Safety of OIT

Patient safety is critical for the commercial success of OIT. Although adverse reactions were frequently reported, most were localized. Some systemic reactions requiring adrenaline injection have been reported[5,6,9,11,12, 15] (Table 2). Importantly, the systemic reactions occurred not only during the dose escalation phase, but also during home administration.[22,23] The overall risk associated with the allergen exposure varies with the characteristics of the population from which the subjects are enrolled. In OIT for severe milk allergy, the incidence of adverse reactions was higher than that observed in other studies.[11] In our trial of OIT with patients who could develop food anaphylaxis, the patients receiving milk OIT showed the highest incidence of moderate and severe reactions, followed by those who with egg and those with wheat allergies.[24] Further trials to investigate the safety of OIT in patients with severe food-induced anaphylaxis are needed.

A systematic review of cow's milk OIT compared to an elimination diet demonstrated the association of OIT with a greater risk of allergic

Table 2. Safety of OIT for food allergy

Food	Study (published year)	Subjects	History of anaphylaxis	Rate of adverse reaction	therapy
Peanut	Varshney et al. (2011)	2-10 years OIT: 19 Control: 9	excluded	Initial day: 47% of the subjects At home: no data	Adrenaline given 2 times for OIT
	Anagnostou et al. (2014)	7-16 years OIT: 39 Control: 46	included	Most events were mild oral itching (6.3% of the OIT doses)	Adrenaline given 1 time for OIT
Milk	Longo et al. (2008)	5-17 years OIT: 30 Control: 30	included	Rush phase: 100% of the subjects At home: 57% of the subjects	Adrenaline given 4 times for OIT
	Skripak et al. (2008)	6-17 years OIT: 13 Control: 7	excluded	45.4% of the OIT doses	Adrenaline given 4 times for OIT
	Pajno et al. (2010)	4-13 years OIT: 15 Control: 15	excluded	80% of the subjects	Adrenaline given 2 times for OIT
Egg	Burks et al. (2012)	5-11 years OIT: 40 Control: 15	excluded	Initial day: 27.4% of the OIT doses At home: 24.2% of the OIT doses	No adrenaline given

reactions that require adrenaline injection or systemic corticosteroid.[25] However, because the study covered a small number of subjects, the greater risk of OIT over an elimination diet remains uncertain.

Tolerability of OIT

The studies cited above demonstrated that OIT for food allergy is effective in increasing the amount of food that treated patients tolerate by 50% or more.[5, 7, 9, 11, 14, 15] However, the long-term effects of OIT are still uncertain.

In fact, it is not yet clear whether the tolerance of those who passed the OFC without receiving therapy can be considered permanent or whether their desensitization is transient. Tolerance is defined as a permanent loss of reactivity correlated with the ability to ingest the offending food in the absence of ongoing therapy without incurring symptoms.[13] On the other hand, desensitization—defined as "a change in the threshold dose of food allergen necessary to cause allergic reactions"—can be either short term or prolonged by ongoing therapy. [26] Little data address the question whether OIT for food allergy induces permanent tolerance or whether the effects represent transient desensitization. Many patients lose desensitization after suspending OIT.[6,9] In a recent study by Keet et al.,[10] 6 of the 15 subjects, who passed a full milk challenge after 60 weeks of maintenance, lost desensitization after 1 and 6 weeks off the therapy. Desensitization is quickly lost when OIT therapy is interrupted. Although it seems likely that maintaining a state of desensitization requires ongoing exposure, we do not know how often patients should ingest foods they were previously allergic to. Previous studies suggested that desensitization induced by OIT does not quickly lead to tolerance. It is possible that a longer period of daily maintenance treatment may be required for most patients to develop tolerance or, at least, similar to the maintenance period for SCIT for inhaled allergens.

Clinical trials of other immunotherapies

Sublingual immunotherapy

SLIT methods involve placing quite small immunotherapy doses under the tongue. The method has been shown effective in the treatment of allergic

Table 3. Clinical trials of novel immunotherapy

Treatment	Allergen	Study (published year)	Subjects	Duration/ Target dose	Clinical outcomes
Sublingual immunotherapy (SLIT)	Peanut	Kim et al. (2011)	1-11 years Active: 11 Control: 7	Duration of therapy: 12 months Target dose: 2000 mg	threshold doses ↑: active group was higher than control group. Drop outs: 0
		Fleischer et al. (2013)	12-37 years Active: 20 Control: 20	Duration of therapy: 44 weeks Target dose: 5000 mg	threshold doses ↑: 70% of active group, 15% of control group. Drop outs: 10
SLIT + OIT	Milk	Keet et al. (2012)	6-15 years Active: 30	Duration of therapy: 60 weeks Target dose: high dose (2 g), low dose (1 g), SLIT (7 mg)	Desensitization: 60% of low dose group, 80% of high dose group, 10% of SLIT group Drop outs: 2
Epicutaneous immunotherapy (EPIT)	Milk	Dupont et al. (2010)	6-15 years Active: 10 Control: 9	Duration of therapy: 3 months Target dose: 300 mg	threshold doses ↑: 60% of active group, none of control group. Drop outs: 0
OIT + Omalizumab	Milk	Nadeau et al. (2011)	7-11 years Active: 11	Duration of therapy: 24 weeks Target dose: 2000 mg	threshold doses ↑: 90% of active group Drop outs: 1

rhinitis.[27] Two randomized, controlled trials of SLIT for peanut have been published[28,29]; Fleisher et al. reported SLIT with peanut in a multi-center, double-blind, placebo-controlled trial[29] in which 40 subjects of median age 15 years old were enrolled. Maintenance doses ranged from 165 to 1386 mg of peanut protein. At week 44 after starting the therapy, fourteen (70%) of 20 subjects who received active treatment had increased their threshold doses of the allergen, but none of the subjects passed the 5 gram of peanut OFC. Additionally, adverse reactions, mostly mild, did not require oral antihistamine administration.

Keet et al. directly compared the efficacy of SLIT and OIT[10] for milk. The study enrolled 30 randomized subjects with milk allergy who received SLIT alone or SLIT followed by OIT. After an initial SLIT escalation, the subjects were randomized, one group would continue SLIT only and the other would begin OIT at two different maintenance doses. Sixty weeks later, only one subject in the SLIT group passed the 8 gram of milk OFC, compared to six in the lower-dose OIT group and eight in the higher-dose OIT groups. Systemic reactions were more common during OIT than during SLIT. Patients with peanut allergy treated with either peanut OIT or SLIT also experienced greater efficacy associated with OIT than with SLIT.[30] These results showed that OIT is more effective than SLIT alone in achieving desensitization. Combination therapy of SLIT and OIT might benefit from the safety of SLIT and the potential for tolerating ever greater doses of food with OIT.

Epicutaneous immunotherapy

Epicutaneous immunotherapy (EPIT) may be a new approach for food allergy. EPIT, which involves the application of an allergen-loaded patch on intact skin, was shown to desensitize milk-allergic patients.[31] Subjects in the active treatment group could tolerate higher doses of milk in OFC during follow-up visits than subjects in the placebo group. Adverse effects consisted mostly of local

skin reactions and included no severe systemic reaction. This pilot study suggests that EPIT is safe and well-tolerated; epicutaneous administration may be an effective option for delivering immunotherapy.

The anti-IgE monoclonal antibody

The anti-IgE monoclonal antibody (omalizumab), a recombinant humanized monoclonal IgE-blocking antibody, works by decreasing or preventing the allergic response triggered by IgE molecules. Adjunct administration of recombinant monoclonal anti-IgE therapy may be a promising strategy to improve the safety profile associated with OIT.[32,33]

Nadeau et al. reported a pilot study of omalizumab treatment combined with milk OIT.[33] After nine weeks of pretreatment with omalizumab alone, a course of OIT with omalizumab was given, followed by a period of maintenance OIT without omalizumab and, finally, a DBPCFC at week 24. Nine of 10 subjects achieved the target dose and passed the DBPCFC. The incidence of adverse reactions, which were mostly mild, was 1.8%. Only one subject developed rhinitis and a generalized urticaria; he responded to adrenaline when tested under a DBPCFC protocol. This result suggests that use of recombinant monoclonal anti-IgE therapy would be effective in reducing severe adverse reactions during the escalation phases of OIT.

Conclusion

OIT can increase the threshold dose to a food allergen and lead to desensitization. Although OIT appears to be an effective new therapy for food allergies, even without tolerance, the evidence for its efficacy and safety in long-term therapy is sparse. Moreover, some novel immunotherapies and routes of administration might be effective for food allergies. SLIT and EPIT show that patients can increase their threshold doses to a food allergen without suffering severe symptoms. Adding anti-IgE monoclonal antibody to OIT therapy reduces the incidence of the symptoms seen during OIT therapy alone. These new therapies have not yet been fully assessed for efficacy; the data available come from only a few studies, which were based on small sample sizes. Further studies are needed before these therapies can be offered to patients in clinical practice.

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References

1. Sampson HA. Food allergy. Part 2: diagnosis and management. J Allergy Clin Immunol. 1999;103:981-9.
2. Sicherer SH, Furlong TJ, Munoz-Furlong A, Burks AW, Sampson HA. A voluntary registry for peanut and tree nut allergy: characteristics of the first 5149 registrants. J Allergy Clin Immunol. 2001;108:128-32.
3. Cohen BL, Noone S, Munoz-Furlong A, Sicherer SH. Development of a questionnaire to measure quality of life in families with a child with food allergy. J Allergy Clin Immunol. 2004;114:1159-63.
4. Oppenheimer JJ, Nelson HS, Bock SA, Christensen F, Leung DY. Treatment of peanut allergy with rush immunotherapy. J Allergy Clin Immunol. 1992;90:256-62.
5. Skripak JM, Nash SD, Rowley H, Brereton NH, Oh S, Hamilton RG, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. J Allergy Clin Immunol. 2008;122:1154-60.
6. Buchanan AD, Green TD, Jones SM, Scurlock AM, Christie L, Althage KA, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. J Allergy Clin Immunol. 2007;119:199-205.
7. Jones SM, Pons L, Roberts JL, Scurlock AM, Perry TT, Kulis M, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. J Allergy Clin Immunol. 2009;124:292-300, e1-97.
8. Meglio P, Bartone E, Plantamura M, Arabito E, Giampietro PG. A protocol for oral desensitization in children with IgE-mediated cow's milk allergy. Allergy. 2004;59:980-7.
9. Blumchen K, Ulbricht H, Staden U, Dobberstein K, Beschorner J, de Oliveira LC, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. J Allergy Clin Immunol. 2010;126:83-91 e1.
10. Keet CA, Frischmeyer-Guerrerio PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. J Allergy Clin Immunol. 2012;129:448-55, 55 e1-5.
11. Longo G, Barbi E, Berti I, Meneghetti R, Pittalis A, Ronfani L, et al. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. J Allergy Clin Immunol. 2008;121:343-7.
12. Staden U, Blumchen K, Blankenstein N, Dannenberg N, Ulbricht H, Dobberstein K, et al. Rush oral immunotherapy in children with persistent cow's milk allergy. J Allergy Clin Immunol. 2008;122:418-9.
13. Scurlock AM, Vickery BP, Hourihane JO, Burks AW. Pediatric food allergy and mucosal tolerance. Mucosal Immunol. 2010;3:345-54.

14. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. Ann Allergy Asthma Immunol. 2010;105:376-81.
15. Burks AW, Jones SM, Wood RA, Fleischer DM, Sicherer SH, Lindblad RW, et al. Oral immunotherapy for treatment of egg allergy in children. N Engl J Med. 2012;367:233-43.
16. Vickery BP, Pons L, Kulis M, Steele P, Jones SM, Burks AW. Individualized IgE-based dosing of egg oral immunotherapy and the development of tolerance. Ann Allergy Asthma Immunol. 2010;105:444-50.
17. Vickery BP, Lin J, Kulis M, Fu Z, Steele PH, Jones SM, et al. Peanut oral immunotherapy modifies IgE and IgG4 responses to major peanut allergens. J Allergy Clin Immunol. 2013;131:128-34 e1-3.
18. Wanich N, Nowak-Wegrzyn A, Sampson HA, Shreffler WG. Allergen-specific basophil suppression associated with clinical tolerance in patients with milk allergy. J Allergy Clin Immunol. 2009;123:789-94 e20.
19. Varshney P, Jones SM, Scurlock AM, Perry TT, Kemper A, Steele P, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. J Allergy Clin Immunol. 2011;127:654-60.
20. Anagnostou K, Islam S, King Y, Foley L, Pasea L, Bond S, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. Lancet. 2014.
21. Ebisawa M, Sato S, Utsunomiya T, Hayashi N, Imai T, Yanagida T. Rush oral immunotherapy for the treatment of hen's egg- and cow's milk-induced anaphylaxis. Translational Science: from Basic to Clinical Immunology and Allergy. 2012:359-64.
22. Hofmann AM, Scurlock AM, Jones SM, Palmer KP, Lokhnygina Y, Steele PH, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. J Allergy Clin Immunol. 2009;124:286-91, 91 e1-6.
23. Varshney P, Steele PH, Vickery BP, Bird JA, Thyagarajan A, Scurlock AM, et al. Adverse reactions during peanut oral immunotherapy home dosing. J Allergy Clin Immunol. 2009;124:1351-2.
24. Sato S, Yanagida N, Ogura K, Nagakura K, Emura S, Asaumi T, et al. Clinical studies in oral allergen-specific immunotherapy: Difference among allergens. Int Arch Allergy Immunol. 2014;Published.
25. Brozek JL, Terracciano L, Hsu J, Kreis J, Compalati E, Santesso N, et al. Oral immunotherapy for IgE-mediated cow's milk allergy: a systematic review and meta-analysis. Clin Exp Allergy. 2011;42:363-74.
26. Rolinck-Werninghaus C, Staden U, Mehl A, Hamelmann E, Beyer K, Niggemann B. Specific oral tolerance induction with food in children: transient or persistent effect on food allergy? Allergy. 2005;60:1320-2.
27. Radulovic S, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. Cochrane Database Syst Rev. 2010:CD002893.
28. Kim EH, Bird JA, Kulis M, Laubach S, Pons L, Shreffler W, et al. Sublingual immunotherapy for peanut allergy: clinical and immunologic evidence of desensitization. J Allergy Clin Immunol. 2011;127:640-6 e1.
29. Fleischer DM, Burks AW, Vickery BP, Scurlock AM, Wood RA, Jones SM, et al. Sublingual immunotherapy for peanut allergy: a randomized, double-blind, placebo-controlled multicenter trial. J Allergy Clin Immunol. 2013;131:119-27 e1-7.
30. Chin SJ, Vickery BP, Kulis MD, Kim EH, Varshney P, Steele P, et al. Sublingual versus oral immunotherapy for peanut-allergic children: a retrospective comparison. J Allergy Clin Immunol. 2013;132:476-8 e2.
31. Dupont C, Kalach N, Soulaines P, Legoue-Morillon S, Piloquet H, Benhamou PH. Cow's milk epicutaneous immunotherapy in children: a pilot trial of safety, acceptability, and impact on allergic reactivity. J Allergy Clin Immunol. 2010;125:1165-7.
32. Lieberman JA, Chehade M. Use of omalizumab in the treatment of food allergy and anaphylaxis. Curr Allergy Asthma Rep. 2013;13:78-84.
33. Nadeau KC, Kohli A, Iyengar S, DeKruyff RH, Umetsu DT. Oral immunotherapy and anti-IgE antibody-adjunctive treatment for food allergy. Immunol Allergy Clin North Am. 2012;32:111-33.