- The effect of per oral immunotherapy treatment in severe IgE mediated milk, peanut and egg allergy in adults.

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Summary

Prospective study on per oral immunotherapy treatment in IgE mediated milk, peanut or egg allergy in adults (≥18 year olds).

1. Background

In Finland, the estimated prevalence of physician-diagnosed food allergy in 1-4 year old children is 9%, and the most common allergen is milk (Pyrhönen K 2009). The overall food allergy has been reported to be 3.7% (Sicherer SH 2006). Hen's egg allergy is among the most common food allergies in childhood. In addition, it predicts later development of allergic disease such as asthma. Most of the egg and milk allergy is transient and disappears in childhood. Currently, the standard of care for food allergy includes strict allergen avoidance. However, oral immunotherapy (OIT) has been under investigation in children milk, egg, and wheat allergy. Previously, induction of clinical egg tolerance has been reported with egg oral immunotherapy in children aged from 3 to 13 years (Vickery BP 2010). In adults, strict avoidance is still the standard care but there is also growing interest in treatment of severe food allergy with oral immunotherapy or anti-IgE (Sicherer SH 2006, Sicherer SH 2010).

In respiratory allergy, the administration of allergen immunotherapy is known to alter the natural history of allergic disease and to induce tolerance against allergens (Durham SR 1999). Oral immunotherapy has been introduced also into treatment of allergic rhinitis with good results. However, there is very little information on oral immunotherapy in severe food allergy in adults and no information on the effect of oral immunotherapy on asthma in adults.

In the study of Buchanan et al., 7 subjects were enrolled into egg oral immunotherapy study (Buchanan AD 2007). All the study subjects (mean age 3.7 years) completed the study. All the study subjects had atopic dermatitis and 43% had asthma. All patients had history of egg-ingestion reactions but none had a history of anaphylaxis to egg. Cumulative egg dose at first treatment varied between 17.6-1012 mg and the initial daily home dose varied

between 25-200 mg. Mean baseline egg-specific IgE-level in the study was 24 kU/L (SD 44 kU/L) and 24-month level 12 kU/L (SD 19 kU/L).

In the study of Vickery et al., 8 patients were enrolled into egg oral immunotherapy study (Vickery BP) (median age 5 years). Of these, 75% had atopic dermatitis and 38% asthma. 6 of these 8 patients completed the study. 83% of these six patients developed allergic symptoms during the initial dose escalation day, and 50% developed allergic symptoms during the build-up phase. The mean baseline egg-white specific IgE level was 25 kU/L.

Allergen components Ara h2 and Ara h6 have been estimated to be the best predictive components for symptomatic peanut allergy. In studies on adults, the threshold for allergic symptoms in the challenge tests pre-OIT have varied from 5-50 mg or from 6-100 mg. In the study of Syed et al. symptom threshold in four adult patients (18- 45 years) before OIT were 6mg (peanut specific IgE 20.9 kU/l), 25mg (peanut specific IgE 20.6 kU/l), 100mg (peanut specific IgE 264 kU/l), 50mg (peanut specific IgE 149 kU/l).

In a Cochrane review on egg allergy it was agreed that OIT can desensitize a large number of egg-allegic patients but the long-term tolerance was unknown. However, sustained unresponsiveness in food allergy has been reported to increase by longer duration of immunotherapy in egg allergy. In a study with 5-18 year old children, sustained unresponsiveness increased from 27.5% (immunotherapy for two years) to 50.0% when OIT was continued for four years.

In the same Cochrane review side effects were brought into discussion since sixty nine per cent of the participants presented with mild-to-severe adverse effects during OIT. Five of the 100 participants required epinephrine. This safety issue has been further studied in peanut allergy OIT, where 352 treated patients received 240 351 doses of peanut and experienced 95 reactions that were treated with epinephrine. Only three patients received two doses of epinephrine and none required more intensive treatment. A total of 298 patients achieved the maintenance dose (thus with a success rate of 85%). In addition to OIT also sublingual immunotherapy has been studied in peanut allergy. OIT was reported to be far more effective than sublingual therapy but also with more adverse reactions.

In milk allergy, accordingly, OIT was more effective than sublingual therapy but also with more adverse reactions. Only one of the 10 patients receiving sublingual therapy passed the milk challenge after immunotherapy. With oral immunotherapy six out of ten (sublingual therapy first and then continued with oral immunotherapy) and eight out of ten passed the milk challenge after OIT. In a Cochrane review on OIT for milk allergy, the conclusions were similar to peanut allergy. OIT is effective but is associated with side effects and long-term tolerance has not been established.

This is the second part of the oral immunotherapy study in adults at Skin and Allergy Hospital. The preliminary results for oral immunotherapy since 2012 are presented in the paragraph 4.

3. Study plan

3.1. Subjects

We study 100 subjects. All subjects are adults having no other severe chronic diseases.

(a) **30** patients (≥18 year olds) that have IgE mediated severe milk allergy

(b) **30** patients (≥18 year olds) that have IgE mediated severe peanut allergy

(c) **30** patients (≥18 year olds) that have IgE mediated severe egg allergy

(d) up to **10** patients whose oral immunotherapy against milk allergy has started as individually given treatment for clinical need

The diagnosis of milk allergy is verified with positive history, skin prick test (>5 mm), egg and milk allergen specific IgE antibodies (>5.0 kU/l). In addition, food allergy is verified with an open label (milk allergy) or blind (peanut and egg allergy) allergen specific challenge test.

Atopic subjects may have simultaneously other allergies. Intermittent mild asthma, and mild and moderate persistent asthma are tolerated and treatment with inhaled steroids and other asthma medication is allowed. Atopic subjects may have additional skin symptoms. Quality of life, anxiety and patient history data is collected by questionnaires. All patients undergo a spirometry with a bronchodilatator test, fractionale exhaled nitric oxide and a methacholine challenge before and a year after oral immunotherapy. Those with test results diagnostic for asthma (FEV1 response in a bronchodilator test > 12%/200ml and/ or PD20 <600 µg/ml methacholine in methacholine provocation test) (Crapo) are treated with asthma medication before hyposensibilisation treatment is started.

Exclusion criteria: adults with instabile cerebrovascular or heart disease, active autoimmune disease or cancer, or current use of betablocking agents. In addition, poorly controlled asthma or FEV1 < 70% (FEV1< -2SD) are not tolerated.

3.2. Allergen specific challenge test

In egg allergy, increasing doses are given every 60 minutes during the egg or peanut allergen challenge. The protocol is done in a double-blind manner (day A, day B and one to seven days in between the two challenge days).

3.2.1. Food challenges.

For milk allergy, increasing doses are given every 60 minutes (5 drops of milk, 1 ml of milk, 10 ml of milk, 50ml and 80 ml of milk). The challenge can be done as an open step-wise challenge during two days (Vlieg-Boerstra 2011).

The given doses in the peanut allergen challenge test are 5mg, 25mg, 50mg, 200mg and 1000mg of peanut protein. The 50mg of peanut protein is similar to ¼ peanut. The maximum dose of 1000mg peanut protein is approximately 5 peanuts.

Accordingly, the challenge test in egg protein allergy is started with 5mg egg protein (150mg of meat ball) and then followed by 25mg of egg protein, 50mg, 500mg and 1000mg of egg protein.

The patient is followed for signs and symptoms of allergic reaction for two hours after the last dose of allergen. In the case of allergic reaction, the patient is treated with normal procedures: 0,5 mg epinephrine im in anaphylaxis, followed by corticosteroids (prednisolon 40mg po, methylprednisolon 40-80mg iv), cetirizin 10mg po and 0,9% NaCl iv, salbutamol and ipratropiumbromide as inhalation (Atrodual® 2,5ml)(Akuuttihoito-opas).

3.3. Study protocol

In milk allergy, increasing doses are given using the following schedule. If the subject does not tolerate a given dose and symptoms are mild, then that dose or the previously tolerated one is repeated, and the protocol proceeds as outlined. If the subject experiences significant symptoms, then the protocol is stopped, and the highest tolerated dose is used as the starting daily one.

The schedule for oral immunotherapy against milk allergy:

Day no	Milk, diluted (1:10 drops)	Milk, dropps	Milk, ml
1	5		
7	10		
14	20		
21		5	
28		10	
35		20	
42			1
49			2
56			5

63	10
70	20
84	40
98	80
112	160
126	200

Similarly, in egg and peanut allergy, increasing doses are given using the predefined schedule. If the subject does not tolerate a given dose and symptoms are mild, then that dose or the previously tolerated one is repeated, and the protocol proceeds as outlined. If the subject experiences significant symptoms, then the protocol is stopped, and the highest tolerated dose is used as the starting daily one.

Product	Week	Dose	Protein (mg)
Egg protein liquid 1mg/ml (vihreä)	**1**	**0,1 ml**	**0,1**
	2	**0,2 ml**	0,2
	3	**0,4 ml**	0,4
	4	**1 ml**	**1**
	6	**2 ml**	2
Egg protein	**8 hoitaja**	**0,4 ml**	**4**

liquid 10mg/ml (punainen)	10	**0,8 ml**	8
	12	**1,2 ml**	12
	14	**2,5 ml**	**25**
	16	**5 ml**	50
	18	**10 ml**	100
	20	**20 ml**	200
Egg protein	**22**	**1 dose (spoon)**	**350**
	24	2 dose	600
	26	3 dose	1050
	32	**3 dose**	**1050**

The schedule for oral immunotherapy against egg allergy:

The schedule for oral immunotherapy against peanut allergy:

Product	Week	Tea spoon or number/day (1 tl=2g)	Protein (mg)
Margarine contain peanut protein	**1 vo**	**1 teespoon**	**0,1**
	2	2	0,2
	3	4	0,4
	4 vo	**1**	**1**
	6	2	2
	8	3	3
	10 vo	**5**	**5**
	12	6	6
	14 vo	**1**	**10**
	16	2,5	25
	18	5	50
Peanut	**20 vo**	**¼ peanut**	**50**
	22 vo	**½**	**100**
	24	¾	150
	26	1 peanut	200
	28 vo	**1,5**	300
	30	2	400
	32 vo	**3 peanuts**	**600**
	34	4	800

All the patients undergoing oral immunotherapy are prescribed with emergency medication such as antihistamine tablets, prednisolon tablets (40mg for three days in adults), epinephrine autoinjector (300 μg per dose) and salbutamol or terbutaline inhalator.

After escalating doses of allergen during the first phase of oral immunotherapy, the treatment is continued with the highest tolerated maintenance dose until one year of therapy. Spirometry with a bronchodilatator test, fractionale exhaled nitric oxide, a methacholine challenge and immunological parameters are studied a year after oral immunotherapy.

After one year of oral immunotherapy we have given the option to be followed further if the patient is willing to continue the immunotherapy. Spirometry with a bronchodilatator test, fractionale exhaled nitric oxide, and immunological parameters are studied once a year if the oral immunotherapy continues.

3.3. 3. Immunological parameters

Serum samples are taken for allergen component evaluation. Egg white specific IgE and ovomucoid and ovalbumin specific IgE (Pharmacia Diagnostics AB, Uppsala, Sweden) before and after one year of oral immunotherapy for egg allergic patients. Casein, α-lactalbumin and ß2-lactoglobulin specific IgE are studied for milk allergy before and after one year of immunotherapy. Similarly, IgE against peanut, Ara h 2, Ara h 3, Ara h 8, and Ara h 9 are studied in peanut allergy.

3.3. 4. Statistical methods

Frequencies, means, medians, proportions and standard deviations are calculated for all the data. Pairwise IgE results, methacholine challenge test results are analyzed using the t-test or Wilcoxon signed rank test. The published reports on milk oral immunotherapy have been done in rather small number of study subjects, of which all have been children. The estimated numbers (50) of study subjects in this study tolerate also withdrawing of some of the subjects.

4. Preliminary results since 2012

Milk allergy

Eight patients (62 %) have continued oral milk immunotherapy from 4 – 96 months with a mean of 23.5 months. Five (38 %) patients in total have discontinued the desensitization due to allergic reactions (4) or pregnancy (1). The dose range of oral immunotherapy at the current time point is from 3 ml (initiation phase) to 130ml (maintenance dose). Maximum dose has been 200ml. Six patients have reached the maintenance dose while two are still on the initiation phase. Overall milk and casein IgE levels have decreased in patients receiving the maintenance dose, indicating a possible decease in immunologic reactions against the allergen.

Egg allergy

Three adult patients have received oral immunotherapy because of severe egg allergy. All these patients are women and their symptom history for egg allegy had persisted already since childhood. Two of them have asthma persisted since childhood. Of these, two patients have continued successfully the therapy. However, exacerbation of atopic eczema has led to decreasing the dose of boiled egg white. With one patient the oral immunotherapy was discontinued because of exacerbation of atopic eczema after one year of immunotherapy. The two patients with beneficial immunotherapy results have been 21 and 20 years old women, when the one with cessaction of therapy was 40 year old.

Peanut allergy

In all peanut allergic patients, the Ara h2 level was increased before the immunotherapy with results ranging from 0.5-324 kU/l. The threshold for allergic symptoms in the challenge tests pre-OIT (oral immunotherapy) has varied from 5 to 50 mg. Oral immunotherapy has led to increased allergen tolerance by means of increasing the threshold for symptoms in our six adult patients. However, one patient had an anaphylactic reaction during OIT at the dose of 50 mg; at the initiation phase and the dose was given at hospital. This prompts careful patient selection and follow-up during OIT for adult patients.

4. Study group

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5. Budget

Costs of patient visits are managed by normal clinical work.

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