MODERN THERAPEUTIC APPROACHES IN FOOD ALLERGY

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ABSTRACT

Food allergy has a growing prevalence in children (6-8%) and represents a worrying public health problem. Despite the numerous controversies regarding the feeding in high atopic risk infants and children with food allergy, there are safe and effective drug therapies, some of them already in clinical trial phase (immunotherapy, anti-IgE agents, recombinant vaccines, *Toll-like* receptors agonists, chemokine and chemokine receptor antagonists).

Key words: food allergy, child, immunologic therapies

Food allergy prevalence is increasing in recent decades, at around 6-8% in children and 3-4% in adults (1), 20% higher in 2007 compared to 1997. It is correlated with significant morbidity by itself and associated disorders (risk of atopic eczema, asthma, allergic rhinitis is four times higher than in the general population), but also increased mortality, being involved in about 35% of deaths by anaphylaxis (2).

Recent advances regarding the complex pathogenesis of the disease shows that it is the result of the loss or lack of achieving oral tolerance to food allergens (3).

Oral tolerance develops early in healthy children through different mechanisms, depending on genetic factors, age, intestinal microbiota, dose of antigen. High doses of allergens induce anergy of T cells in the absence of co-stimulatory signals (IL_2, CD_{28}/ $CD_{80,86}$ interaction) and/or deletion of T lymphocyte-mediated by FAS induced apoptosis. Repeated exposure to low doses of allergen stimulates regulatory T lymphocytes: Th_3 (secreting TGFβ) TR_1 (secreting IL_{10}), CD_4CD_{25} (secreting βTGF, IL_4 and IL_{10}).

The most studied are CD_4CD_{25} T cells derived from the thymus, peripheral and mesenteric lymph nodes. Their suppressive phenotype is due, in most part, to the transcription factor $FOXP_3$ expression; therapeutic implications for allergen specific immunotherapy are very important. Determinants of food allergy are low number or inadequate activity of CD_4CD_{25} T lymphocytes, mutation of $FOXP_3$ transcription factor or filaggrin, gastrointestinal epithelium dysfunction produced by "physiological" immunological immaturity in young children or due to exposure to viral/bacterial infections, alcohol, NSAIDs, antacids in older children and adolescents.

Current possibilities for the prevention of allergic sensitization in infants with high atopic risk are limited and controversial. *Hypoallergenic diet in atopic pregnant women* is not accepted because it was shown not to reduce the risk of allergic disorders in childhood (4) and involves the risk of maternal and fetal malnutrition; moreover, transfer of maternal food allergens to fetus seems to play a role in the oral tolerance induction. *Breast milk* remains the ideal food for infants during the first months of life. *Hypoallergenic diet* in women *during lactation* didn't prove a protective effect on allergic diseases of children; recent studies suggest that daily exposure to low doses of β lactoglobulin in breast milk may promote tolerance to cow's milk (5). In case of maternal hypo/agalactiae, the small infant must be fed with *partially hydrolyzed formulas*. Extensively hydrolyzed formulas are inadequate for prevention because they are not tolerogenic.

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Complementary foods should not be introduced before 17 weeks and not later than 26 weeks in atopic infant diet (6).

Current therapy in food allergy consists in avoiding specific food responsible for the symptoms, early recognition of the allergic reaction signs and prompt drug therapy. The impact of disease on quality of life of children and the family depends on the responsible food, severity of past allergic reactions (an anaphylactic accident rises to 94% risk of its recurrence, child and family anxiety), the number of restricted food (influences adherence to the elimination diet), the existence of other allergic co-morbidities requiring specific concomitant therapy (allergic rhinitis, asthma, atopic dermatitis), age (7).

Despite the numerous controversies regarding atopic and allergic infant feeding, there are promising, safe and effective drug therapy, some already in clinical trial phase (specific allergen immunotherapy for small ages, anti-IgE agents, recombinant vaccines, agonists of Toll-like receptors, chemokine and chemokine receptor antagonists). These therapies aim to achieve desensitization or induction of oral tolerance and reduce the risk and severity of allergic reactions.

TABLE 1. *Modern therapies in food allergy (adapted from 2)*

Specific allergen therapies	Nonspecific therapies
Clinical trials • (Subcutaneous, oral, sublingual, epicutaneous) immunotherapy • Extensively heated protein diet • Modified recombinant food protein vaccines Preclinical trials • Antigen- coupled splenocytes • Peptide immunotherapy • Plasmide-DNA immunotherapy	Clinical trials • anti-IgE m-Ab • anti-IL_5 m-Ab • *Trichuris suis ova* Preclinical trials • Toll like -9 receptors agonists • *Lactococcus lactis* (IL_{10}, IL_{12})

Specific allergen immunotherapy is the only curative therapy in IgE-mediated allergic diseases. It proved benefits (low symptom score, serum specific IgE, histamine release from basophiles, Th_2 cytokines production: IL_4, TNF-α, increased IFN γ and specific IgG_4) in allergic rhinitis, asthma and hymenoptera venom allergy (8).

In food allergy, oral tolerance induction for peanuts in the early 1990s was only partially successfully, but accompanied by unacceptable side effects (13.3 to 39%). Genetically engineered modification of allergenic extracts showed a reduction of 35-85% of the IgE binding (9) and there are encouraging results (efficiency 75-86%) in some recent studies (10).

Immunotherapy may result in desensitization or obtaining permanent oral tolerance.

Status of **desensitization** is characterized by obtaining a tolerance to a certain amount of allergen administered with a preset protocol and loss of this effect if the allergen intake is reduced or interrupted. Loss of desensitization is favored by increased intestinal permeability through exercise, viral gastroenteritis or perturbation of the intestinal microbiota (prolonged/repeated courses of oral antibiotics), stress, etc.

Permanent oral tolerance allows discontinuities in allergen ingestion without allergic symptoms. This status is correlated with the development of regulatory T cells and Th_2 immune deviation. $FOXP_3$ transcription factor is critical for regulatory T cell function and maintenance of peripheral tolerance. $FOXP_3$ mutations are responsible for the failure of immunotherapy. It is not proved the correlation of the benefits with the duration of the immunotherapy or some unknown individual factors (11).

Side effects can be local or systemic, exacerbating by exercise, febrile acute diseases, a jeun dose intake, poor control of the concomitant asthma. Most of the side effects are mild/moderate, predominantly affecting the oropharyngeal area (itching, tingling). Severe adverse reactions (hives/angioedema, wheezing, respiratory failure, laryngeal edema, nausea and repeated vomiting, abdominal pain) require cessation of therapy (12).

Children with persistent food allergy (nuts, fish, seafood) characterized by an increased mortality, even after very small accidental doses are eligible for immunotherapy. The risk of adverse reactions is higher and the efficiency is lower in persistent allergies.

Subcutaneous immunotherapy (SCIT) exerts its beneficial effects by stimulating immunosuppressive CD_4CD_{25} T cells, production of IL_{10} or TGF-β, allergen-specific Th_2 cell apoptosis, reduction of tissue mast cells and serum levels of TNF-α and IL-1β (8). SCIT has proved efficiency in peanut desensitization in patients with history of anaphylaxis through increasing the tolerated dose of 178 mg (about half a peanut) to 2805 g (about nine peanuts). The proportion of systemic reactions is about to 39% (13). Peptides and genetic engineering produced proteins are used in some current clinical trials.

An alternative to ITSC is the ***epicutaneous immunotherapy (ECIT***) by applying a soluble allergen cutaneous patch which is absorbed through the *stratum corneum* (14). Epidermis, a non-vascularized stratified epithelium is immunological "supervised" by keratinocytes and Langerhans cells, the latter playing an important role in allergen capture and T cells activation. Experimental studies in mice sensi-

tized to peanuts gave encouraging results (15); in human clinical trials are underway. Dupont, 2010 reported increasing tolerance to milk in children (three months to 15 years) at 1.7 ml/day to 23.16 ml/day in a period of 3 months of ITEC (16).

Oral immunotherapy involves the ingestion of very small amounts of food as a powder or in a food-vehicle (for example, apple juice). The doses are gradually increased over a period of several weeks to achieve the maintenance dose which is administered for several months or years. Start-dose is milligrams order and the maintenance dose – grams. The first successful report dates from 1908 in a boy with egg-triggered anaphylaxis (17). The results of studies that have evaluated the effect of oral immunotherapy are encouraging; its efficiency is 75-86% (18). Longo et al reported cow's milk desensitization in 90% of cases in a group of children with a history of anaphylaxis: 37% tolerated 250 ml and 53% tolerated between 5 and 150 ml of cow's milk after one year of treatment. However, there were recorded adverse effects (60% of cases) that required oral corticosteroid administration (100% of cases), nebulized epinephrine (35% cases) or intramuscularly epinephrine (6% of cases) (19).

An alternative to classical oral immunotherapy is the use of the extensively heated food proteins. Clinical trials have achieved asymptomatic ingestion of cooked egg and milk in children who do not tolerate raw foods. Their regular ingestion was followed by reducing the size of the skin allergy testing response, increased serum specific IgG4, allergen-specific T regulatory cells number, suppression of basophiles, decreased IgE binding epitopes, suggesting that this method could be a natural and safe alternative to oral immunotherapy (20).

Sublingual immunotherapy (SLIT), safe and effective in respiratory allergy seems also to be an attractive therapy in food allergy. SLIT involves placing sublingual food in a liquid form for about 2 minutes, then swallowing it. Starting dose is much higher than in OIT. The advantage of ITSL *vs*. ITO is gastric allergen digestion avoidance and lower percentage of side effects because gastric mucosa contains Langerhans cells, tolerogenic antigen presenting cells and a small number of effectors (12). Since 2003 when the first attempt of SLIT had been reported in a patient with anaphylaxis to kiwi, numerous studies on peanuts, peaches, milk and peanuts allergy had been published. Kim et al have obtained desensitization on a lot of 11 children with peanut allergy after six months of SLIT with a 1710 mg tolerated dose (21).

Although immunotherapy results seem to be encouraging, randomized studies are needed to assess accurately the effectiveness and safety, technical standardization (extracts used protocol implementation, duration), to determine if clinical improvement is due to the induction of oral tolerance or desensitization.

Recombinant modified „vaccines"

Genetic engineering provides small peptides containing epitopes of the major allergens, but with reduced ability to cross-linking to the IgE receptors on basophiles and mast cells (peptides less than 30 amino acids are not able to bind to the IgE receptors located on the effectors cells) (22). These peptides retain therapeutic benefits, but are less aggressive in terms of side effects that can cause activation by specific immunotherapy. Apple allergens (Mal d1), peanut (Ara h1, Ara h2 , Ara h3), milk (casein), fish (parvalbumin), peach (Pru p3) are the object of the current researches (22). Modified food proteins can be coupled with bacterial adjuvants such as *Listeria monocytogenes* or heat-inactivated *E coli* nonpatogenic in order to obtain the Th_1 phenotype switch (1). There is a vaccine undergoing clinical trial for rectal administration (EMP -123) containing three modified recombinant proteins (Ara h1, Ara h2, Ara h3) encapsulated with *E coli* (2).

Anti-IgE agents

Humanized monoclonal antibody could be linked to IgE molecule in order to prevent coupling of high affinity receptors on the surface FcεRI basophiles and mast cells and low affinity receptors FcεRII on B lymphocytes, dendritic cells and intestinal epithelial cells. The first study on the use of anti - IgE in food allergy dates from 2003; mIgG1 subcutaneous anti- IgE antibody, TNX -901 (Talizumab) at doses of 150, 300 or 450 mg every 4 weeks (4 doses) in a group of 84 patients with peanut allergy has allowed to increase the dose of allergen tolerated in a dose-dependent manner, decrease total serum IgE value and seems to be a therapeutic perspective to reduce the risk of severe allergic accidents (22). Omalizumab use in peanut allergy could be able to obtain oral tolerance (1 g after 24 weeks) in 44% of cases (2).

There are some ongoing studies whose preliminary results show that anti- IgE therapy followed by oral immunotherapy allows faster desensitization with reduced side effects than single immunotherapy.

Chemokines and anti-chemokines receptors

Intravenous administration of humanized anti-IL_5 antibodies in eosinophilic gastroenteritis was followed by the decrease of circulating and tissue eosinophils, but not clinical improvement. Multi-

center studies are ongoing to evaluate the safety and tolerance in the same disease of the mepolizumab (anti- IL_5) administration with demonstrated clinical effectiveness studies in adults (23).

Administration of recombinant $IL_{12,}$ cytokine which stimulates the development of Th_1 cells and inhibit the Th_2 phenotype switch was followed by a decrease in serum and sputum eosinophils in asthmatic patients. Systemic toxicity limits the practical application (22).

In **conclusion**, the possibilities of ante/postnatal food sensitization prophylaxis in children with atopic risk are controversial. Current knowledge on the development of oral tolerance contradicts classical strict allergen avoidance. Immunotherapy is a future hope for persistent food allergy; patients will be genotyped for $FOXP_3$ regulatory T lymphocytes mutations.

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