EDITORIAL

FOOD ALLERGY: ORAL TOLERANCE OR IMMUNOTHERAPY?

Foods are able to cause reactions through different mechanisms (immunoallergic, enzyme deficiencies, toxicity) – the clinical, diagnostic and health care problems of which are the source of considerable controversy[1]. At nomenclature proposed by the EAACI (European Academy of Allergology and Clinical Immunology) under the concept "food hypersensitivity" include reactions acknowledged from the outset as being of a "non-allergic nature", while "food allergy" is defined as a reaction that may be "IgE mediated" or "non-IgE mediated"[2,3]. However, it should be accepted that IgE mediated type I hypersensitivity reactions are the phenomena commonly taken to constitute genuine allergic reactions – these being candidates for specific treatment. To this effect, it is advisable to identify the causal antigens contained in each food.

As a consequence of cooking, food suffers biochemical alterations secondary to important temperature changes (cooking, boiling, freezing) and mixing with elements that can modify the biochemical composition (vinegar, certain spices). Posteriorly, following ingestion, food undergoes further transformation, including release of the protein components that give rise to sensitization phenomena in susceptible individuals – with the resulting allergic reactions, fundamentally at skin level (urticaria, angioedema, eczema), but also within the gastrointestinal and respiratory tracts. However, the most serious events are anaphylactic reactions, which may prove life-threatening. Nevertheless, identification has been limited to only allergenic proteins or the epitopes of certain foods such as milk and eggs – which along with fish and nuts are the elements that most often deviate the host immune response, activating the Th2 lymphocytes and thus inducing the production of specific IgE antibodies, being outstanding the conformational nature and repetitive display of epitopes on allergens, the digestion resistant proteins, or the persistence of digestion labile proteins in an intact conformation during the gastrointestinal transit[4-7].

The anatomical and functional integrity of the gastrointestinal barrier guarantees the normal digestion and absorption of food, and its tolerance – particularly as refers to proteins with the potential to act as potent allergens. Alterations in these mechanisms may affect the epithelial cells, intercellular permeability, dendritic cell function (antigen-presenting), M cell from Peyer patches, or elements that intervene in immune defense – the T_H3, T_r1 or $CD4^+$ $CD25^+$ cells[7,8]. The alteration of one mechanism or other can give rise to intolerance reactions (not mediated by IgE) or allergic responses mediated by IgE (in atopic individuals) – both phenomena being encompassed within the concept of hypersensitivity[2].

Some foods (particularly cow's milk and egg) become tolerable after a period of time without consuming such products, as is observed in a large percentage of children in

those situations where the phenomenon develops in early infancy – though this is not seen in all cases. In general, intolerance of other foods persists throughout life in most patients, particularly when sensitization occurs in older children or in adults[9,10]. As a result, the long-term prognosis is uncertain, and this warrants the application of methods designed to induce tolerability or desensitization.

Spontaneous tolerance of foods that have caused clinical reactions may be due to anatomic-functional restructuring of the digestive barrier secondary to a maturation process. This would explain the above mentioned favorable evolution of milk and egg intolerance in most children, whether mediated by IgE antibodies or not. The persistence of sensitization in atopic children is more likely when the familial incidence of atopy is more manifest – due to the importance of this genetic predisposing factor in the prevalence of allergic disease. In those subjects where food allergy persists, the risk of new sensitization phenomena is high, particularly as refers to aeroallergens that cause rhinitis, rhinoconjunctivitis and/or asthma, i.e., diseases commonly found in these patients[11].

The usual management approach is to eliminate from the diet those foods that have been well identified as being responsible for the clinical manifestations. However, out of carelessness, improvidence or a lack of awareness, it is difficult to completely avoid the ingestion of certain foods that are sometimes included in the composition of commercial recipes or products, and are not clearly stated on the labeling (occult foodstuffs). Hence the attempts to induce food tolerability, based on careful testing of the ingestion of progressive amounts of food (tolerance), or desensitization through immunotherapy.

With either procedure, in IgE mediated food allergy, desensitization should be achieved by restoring a normal immune response, in the same way as in aeroallergen immunotherapy[12]. It is not clear how the induction of tolerance via the oral route occurs. Some studies have reported a reduction in specific IgE[13,14] and an increase in specific IgG4, in the course of tolerance testing – a situation that may be related to the desensitization mechanism[15]. However, the induction of tolerance via the oral route has a number of inconveniences. It seems that tolerance is only achieved of the food being tested, though not of other foods when more than one product is implicated. Accordingly, Niggemann et al[15] have proposed the term "specific oral tolerance induction" (SOTI), in reference to such procedures. On the other hand, it is doubtful whether the resulting tolerability is long-lasting[16]. In some cases tolerance is only achieved of minimum amounts of the causal food – as a result of which the risk persists if the dose is exceeded[14]. In addition, with ingestion – even in progressive amounts – important reactions may occur. As a result, it is advisable to apply the technique in hospital. To summarize, although this procedure is effective in some patients, there is no guarantee that the results will be permanent, or that new sensitizations will be avoided – though application can be decided in some cases.

Immunotherapy offers greater expectations. When applied by subcutaneous route, immunotherapy is highly effective in securing aeroallergen desensitization. Furthermore, the technique is usually well tolerated and avoids new sensitizations. The underlying mecha-

nism of action is quite well known, though certain gaps in knowledge remain. In this context, the restoration of Th1/Th2 lymphocyte balance is observed in treated individuals[12]. Nevertheless, while attempts to administer immunotherapy via the subcutaneous route with foods has proven effective in a considerable number of patients, there are many adverse reactions. This approach is therefore not recommended[15].

The sublingual route constitutes the alternative. This approach has been introduced more recently, and appears to be effective with aeroallergens – though the mechanism of action has not been fully clarified to date[17]. Recent publications involving foods suggest that the sublingual route in immunotherapy may be ideal for reducing food sensitization. Enrique et al[18], in a double blind study of adults with hazelnut allergy mediated by IgE antibodies (confirmed by oral provocation tests), employed biologically standardized hazelnut extract. After five months of treatment increased tolerance of provocation was seen in the treated patients versus the control group. A discrete reduction in specific IgE was recorded in both groups, as well as a slight increase in specific IgG4 and IL-10 in the active treatment group. Possibly, with the continuation of treatment, these results may become more evident, as has been reported by Kerzl et al[19], in a patient with severe reactions to kiwi ingestion. This patient was subjected to sublingual immunotherapy for 6 years, resulting in good tolerance with an evident immune response – evidenced by Western blot testing as a clear reduction in IgE reactive to the dominant allergen in kiwi (Act c 1) and an evident increase in IgG4 targeted to the same protein. Likewise at earlier ages, the persistence of sensitization to cow's milk appears to respond favorably to sublingual immunotherapy, as has been demonstrated by Boissieu and Dupont[20] in 7 children between 6 and 17 years of age, subjected to oral provocation before and after 6 months of treatment – though no modifications were observed in the serum specific IgE levels.

To summarize, sublingual immunotherapy is very probably more effective and free of risks than the induction of tolerance via the oral route, in those cases where food sensitization persists beyond early infancy, in view of the known favorable spontaneous evolution of allergy to milk and egg in the first years of life. Logically, confirmation of this principle will require greater accumulated experience and the conduction of well designed studies.

F. Muñoz-López

References

1. Muñoz-López F. Controversies in food allergy. Editorial. Allergol et Immunopathol. 2006;34:43-5.
2. Johansson SGO, Hourihane JO'B, Bousquet J, Bruijnzeel-Koomen C, Dreborg S, Haahtela T et al. A revised nomenclature for allergy. An EAACI position statement from de EAACI nomenclature task. Allergy. 2001;56:813-24.
3. Muñoz-López F. Nomenclature: terminology on the line. Editorial. Allergol et Immunopathol. 2004; 32:183-5.
4. Bernhisel-Broadbent J. Allergenic cross-reactivity of foods and characterization of food allergens and extracts. Ann Allergy Asthma Immunol. 1995;75:295-303.

5. van Do T, Elsayed S, Flovaag E, Hordvik I, Endresen C. Allergy to fish parvalbumins: studies on the cross-reactivity of allergens from 9 commonly consumed fish. J Allergy Clin Immunol. 2005;116:1314-20.
6. Arlian LG, Morgan MS, Quirce S, Marañon F, Fernández-Caldas E. Characterization of allergens of *Anisakis simplex*. Allergy. 2003;58:1299-1303.
7. Untersmayr E, Jansen-Jarolin E. Mechanisms of type I food allergy. Pharmacol Ther. 2006;112:787-98.
8. Chehade M, Mayer L. Oral tolerance and its relation to food hypersensitivity. J Allergy Clin Immunol. 2005;115:3-12.
9. Wood RA. The natural history of food allergy. Pediatrics. 2003;111:1631-7.
10. Cantani A, Micera M. Natural history of cow's milk allergy. An eight-year follow-up study in 115 atopic children. Eur Rev Med Pharmacol Sci. 2004;8:153-64.
11. Saarinen CM, Pelkonen AS, Mäkelä MJ, Savilahti E. Clinical course and prognosis of cow's milk allergy are independent on milk-specific IgE status. J Allergy Clin Immunol. 2005;116:869-75.
12. Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. J Allergy Clin Immunol. 2007;119:790-9.
13. Martorell, A, Toledo RF, Cerdá JC, Martorell A. Oral rush desensitization to cow milk. Following of desensitised patients during three years. Allergol et Immunopathol 2007;35:174-6.
14. 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.
15. Niggemann B, Staden U, Rolinck-Werninghaus C, Beyer K. Specific oral tolerance induction in food allergy. Allergy. 2006;61:808-11.
16. Roling-Werninghaus C, Staden U, Mehl A, Hagelmann E, Beyer K, Niggemann B. Specific oral tolerance induction with food in childrIn: transient or persistent effect on food allergy? Allergy. 2005;60:1320-2.
17. Moingeon P, Batard T, Fadel R, Frati F, Sieber J, van Overtvelt L. Immune mechanisms of allergen-specific sublingual immunotherapy. Allergy. 2006;61:151-65.
18. Enrique E, Pineda F, Malek T, Bartra J, Basagaña M, Tella R et al. Sublingual immunotherapy for hazelnut food allergy: a randomised, doble-blind, placebo-controlled study with standardized hazelnut extract. J Allergy Clin Immunol. 2005;116:1073-9.
19. Kerzl R, Simonowa A, Ring J, Ollert M, Mempel M. Life-threatening anaphylaxis to kiwi fruit: protective sublingual allergen immunotherapy effect persists even after discontinuation. (Letter to Editor). J Allergy Clin Immunol. 2007;119:507-8.
20. Boissieu D, Dupont C. Sublingual immunotherapy for cow's milk protein allergy: a preliminary report. Allergy. 2006;61:1238-9.