



EDITORIAL

## Oral immunotherapy in food allergy: Present and future<sup>☆</sup>



### Inmunoterapia oral en la alergia a alimentos: presente y futuro

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Food allergy (FA) is an important and frequent health problem in our children, and, in Europe, cow's milk proteins (CMP) and hen's egg proteins (HEP) are the main offenders.<sup>1</sup> The risk of anaphylaxis in IgE-mediated FA is high.<sup>2</sup> Its impact on children and on their environmental quality of life, as well as the nutritional aspects, should not be dismissed. Resolution of symptoms during strict avoidance and their reappearance during the double blind placebo control food challenge (DBPCFC) remain the gold standard for the diagnosis of FA.<sup>1</sup> Until very recently, a single approach was available for the treatment of food allergy: avoidance of the offending food. From our point of view, this approach only represents a lack of treatment and it also leaves the child unprotected from hidden or small amounts of the offending food.

The largest immune organ in the body is the intestine. It is constantly working to protect our body from pathogens and also from external proteins. Oral tolerance is an active immunological process which makes the intestine unresponsive to any food, while

FA is the result of its breakdown. The mechanisms involved in the development of oral immune tolerance remain unclear but they seem to depend basically on age and dose of the administered food. The main immunomodulatory cytokines in the gut are IL-10 and TGF- $\beta$  and in this milieu antigen-specific regulatory cells (CD4<sup>+</sup>CD25<sup>+</sup>FOXP3<sup>+</sup>) are essential. In a genetically predisposed child, those cells and cytokines are not present (or in low numbers) in the gut and the development of FA becomes a fact.

Lately, some protocols on oral immunotherapy (OIT) are being investigated in Reference Centers. OIT has as its first aim to increase the amount of food that the child can tolerate without reacting to it, i.e. preventing anaphylaxis. This is usually achieved with the consumption of small amounts of the allergen. Another aim of this technique is to reach a desensitization state, which allows the child to follow a "normal" social life and to achieve an adequate nutritional state. And, finally, the goal of reaching permanent tolerance is of great interest. At this point, it is very important to distinguish between the terms "desensitization" and "tolerance". A child is desensitized to a specific food when he/she goes on eating that food daily with the previously recommended amounts, and no reactions are elicited. Moreover, a child becomes tolerant to a specific food when, once the daily intake of the

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food has been interrupted, he can eat it, whenever he wants, without reactions. So, the ultimate goal of food allergy therapy is permanent oral tolerance.

Before starting OIT, an oral food challenge (OFC) should be performed,<sup>1</sup> to assure that the child is still allergic to that food (although skin prick test and s-IgE remain positive). Parents of all children must sign an informed consent, and the procedure must be approved by the ethics hospital committee. Once allergy is established, the procedure starts with a build-up phase in which small amounts of the diluted food are given to the patient at Hospital. Emergency medications including epinephrine, hydroxyzine, salbutamol and prednisone must be available, and possible symptoms to be evaluated are itching, urticaria, angioedema, exacerbation of eczema, rhinitis or conjunctivitis, dyspnea and wheezing, vomiting, diarrhea and hypotension. Once discharged, the patient must receive the exact amount of the food, daily, at home. The doses are slowly (usually weekly) increased at the out-patient Clinic, until a usual amount of the food is reached (maintenance phase). The food must be taken daily at home and other amounts of the same protein can be eaten, although always separately from the dose. The dose should never be given on an empty stomach. Patients are recommended to avoid exercise for 3 h after the food intake. If there is an intercurrent illness, the dose is not increased, and the previous dose is repeated.<sup>1</sup> This is a time-consuming procedure in which the commitment and compliance of the child and the families are crucial.

In many countries OIT protocols have been developed and research on this area is becoming an important feature in pediatric allergy. Milk and egg allergies are the most frequently treated allergies regarding this approach. Most of the international publications show successful desensitization rates which range from 60% to 100% in different studies. But the acquisition of real tolerance remains unknown as there are only a few studies which evaluate the outcome after the discontinuation of the daily intake of the food. Peanut has also been lately a target for OIT and some encouraging results have been published, although the safety is a big concern. Other foods are under research with no results available yet. The main problem regarding OIT is the possibility of adverse events. These are frequent and sometimes severe. During the last two years, two publications<sup>3,4</sup> gave a view on egg (study on 51 patients) and milk (study on 81 patients) OIT adverse events: most of the patients suffered adverse events (95% in cow's milk allergy and 90% in egg allergy), although frequency was low in relation with the administered doses (6.6% and 7.6%, respectively). Most of the OIT reactions were mild (grades 1 and 2) although some patients suffered grade 4 reactions. Respiratory adverse events were more frequent

during cow's milk OIT, while gastrointestinal reactions were more frequent during egg OIT. These results emphasize the need for well-trained medical personnel and adequate hospital facilities (intensive care unit) available if this treatment is to be followed. On the other hand, for the subgroup of anaphylactic patients, the odds of ever outgrowing the allergy are small and the risk of future severe reactions high. Under these circumstances, this approach would be justified: the more severe the food allergy is and the more common the implicated food, the better the cost/benefit ratio is for OIT approach, including anaphylactic patients.<sup>1</sup>

The use of concomitant treatments such as omalizumab (anti-IgE monoclonal antibody) has also been studied, the results being encouraging. But some questions arise: when should omalizumab be discontinued once desensitization/tolerance has been reached? Can the health system afford the expense? Other approaches are sublingual (peach and hazelnut) and epicutaneous (still under development) immunotherapy. And, finally, the use of heated allergens seems to be a valuable method of specific food desensitization. Traditionally, food allergic children are advised to avoid all forms of specific treated proteins in their diets. Lately, some studies encourage the ingestion of baked egg and milk in allergic patients, under the hypothesis that the heating of proteins on a cereal matrix destroys conformational epitopes decreasing allergenicity. This is an invigorating new pathway as it has been shown that these treated foods can hasten the acquisition of desensitization/tolerance to that specific food, measured by clinical responses and immunological changes.<sup>5</sup> Nevertheless, patients should be chosen carefully.

In conclusion, food allergy is a frequent and important problem in our children. Avoidance of the specific food represents only a lack of treatment which leaves the child exposed to hidden proteins with the potential risk of anaphylaxis, as well as nutritional deficiency and social exclusion. OIT methods are being investigated with promising results which encourage the researchers to find the correct pathway, although adverse events should not be dismissed. Common protocols between Reference Centers should be designed.

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