

Oral Immunotherapy in Food Allergy: Current Situation

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Food allergy (AA) affects a significant number of children and adults, with prevalence figures ranging from 2% to 10% of the population [1], and which are increasing in recent decades [2]. In our environment, those implicated in order of frequency are chicken eggs, cow's milk, fish, legumes and fruits and nuts [3].

The recommended treatment to avoid the appearance of symptoms is the realization of a diet free of the food involved until tolerance is established, which occurs spontaneously in up to 83% of those allergic to cow's milk at the age of four and in the 60% of those allergic to eggs at five years [4]. The adherence to the avoidance treatment is high, but the real feasibility and, therefore, the total efficacy of the indicated treatment are difficult to achieve. The consequences of accidental or inadvertent ingestion are of variable severity [5], so that patients and their caregivers must be trained in the recognition and treatment of adverse reactions. When food allergens are common products, it is polysensitization to several food groups, or products that can be consumed in a hidden way, the exclusion diet produces in itself an important direct and indirect psycho-emotional and economic impact that has only recently been quantified.

For all these reasons, a little more than a decade has been working on the artificial induction of tolerance to food. After severe adverse reactions with subcutaneous parenteral immunotherapy [6], we have chosen to use the oral route [7-9] and there are some experiences with the sublingual route [10,11]. The treatment consists of administering the food allergen causing the symptoms, starting with minimal amounts and increasing them progressively until reaching the normal ration for age. The objective is to reach a tolerance ad libitum or at least increase the amount of food that provokes clinical reactivity, achieving a free diet or sufficiently safe to allow a life without limitations and without adverse reactions.

Efficacy of immunotherapy with food

The published results regarding efficacy are encouraging, reaching tolerance in up to 70 - 90% of treated patients, including patients with high sensitization. As soon as the food is tolerated, frequent, even daily, ingestion of the food is recommended, incorporating it into the normal diet of a healthy subject. To consider that healing has been achieved, this tolerance must be permanent regardless of the frequency and regularity of consumption. A transient tolerance would be equivalent to a desensitization similar to that performed in patients with an adverse drug reaction and in which a lack of transient response is induced, which momentarily allows treatment but is lost when the administration is suspended.

Since the foods that are addressed in childhood are mainly cow's milk and chicken eggs, which are included in different preparations in our diet, the risk of abandoning consumption is small but possible [12]. In some clinical trials [13], the systematic suspension of food has been included for a few months once tolerance has been reached and frequent relapses are found. Currently, it is not known what parameters allow to predict who will develop a persistent or transitory tolerance. Therefore, it seems essential that, once the amount of habitual consumption (a glass of 150 - 200 milk, one unit of egg), which are arbitrarily decided according to gastronomic customs, is maintained during a period of time that is not known exactly but which is empirically advised for at least one year.

In this editorial, we include a critically assessed article [14] about a study [15] in which egg-allergic, non-anaphylactic patients are administered immunotherapy with egg extracts. After reaching tolerance, egg ingestion is suspended for 4 - 6 days. weeks and in later reprovocation with overload (10g of white powder plus one boiled egg) only 37.9% tolerated without problems. Of this group, 41% corresponded to children who had demonstrated early tolerance at 10 months and 11% to those who only achieved it later, which could indicate different phenotypes and imply different attitudes to be taken.

Safety of immunotherapy with food

During the performance of this procedure, adverse reactions are frequent. The frequency of serious reactions is approximately 30% of those included and of slight reactions of 70%. Therefore, its use is limited to professional experts in the recognition and treatment of allergic reactions and must be carried out with adequate medical control. But, even once tolerance is reached, reactions to food are not infrequent in the first few months, coinciding with stimuli such as infection, exercise, emotional stress, ingestion of anti-inflammatory drugs, menstruation and sometimes without specific triggering. The later tolerance continues being good and does not motivate the suspension of the food, but these specific situations indicate that the alert must be maintained. For all these reasons, the results of some meta-analyzes, although favorable to this treatment, advise prudence and the need to assess each case individually. The sublingual route seems safer but less effective and there are fewer experiences [16]. The different immunotherapy guidelines can be consulted in table 1.

<p>Presentation of the allergen used</p> <p>Orally/Sublingual without ingestion</p> <p>Food as it is consumed: liquid milk/raw egg/solid fresh fruit or juice. Available domestic use.</p> <p>Powdered food: complete commercial dehydrated Available domestic use (pre-filled doses).</p> <p>Complete pasteurized liquid food or more allergenic part (full or light egg) Available for domestic use.</p> <p>Fruit extract (lipid transfer protein) LTP. Prepared for commercially available immunotherapy for treatment.</p> <p>Extract dried fruits prepared ad hoc for immunotherapy. Not available commercially.</p> <p>Subcutaneous</p> <p>Commercial extract for immunotherapy.</p> <p>Ad hoc extract for immunotherapy (not commercially available).</p> <p>Epicutaneous</p> <p>Dehydrated natural food presentation powder. You need specific epicutaneous cameras.</p> <p>Time</p> <p>Slow/Fast. From days to years.</p> <p>A daily dose</p> <p>Several daily doses.</p> <p>Initially grouped in several daily doses and subsequently weekly.</p> <p>Two daily doses widely separated several hours.</p> <p>Place</p> <p>Two daily doses widely separated several hours.</p> <p>Joined.</p> <p>Day hospital in semi-hospital regime.</p> <p>All doses in consultation.</p> <p>Increments always in consultation and maintenance at home.</p> <p>Increases in consultation and address.</p> <p>Previous medication</p> <p>None except for treatment of comorbidity symptoms.</p> <p>Antihistamines</p> <p>Cromolyn</p> <p>Omalizumab.</p>

Table 1: Different types of guidelines used in immunotherapy with food.

Food and ages

Most authors address persistent milk and egg allergies. That is, it is used as an exceptional procedure when spontaneous evolution has not arrived and it is a difficult food to avoid. Occasionally other foods are addressed, including some relatively "expendable" such as some fruits or certain vegetables. The need to maintain a frequent intake in a habitual way limits the interest that the action can have in these cases beyond the experimental model. An exception would be nuts, mainly peanuts in patients with anaphylactic sensitization, who cannot avoid their contact or who have repeatedly suffered very serious symptoms [17] despite the precautions taken.

Alternatively, in Spain, the Spanish Society of Clinical Immunology and Pediatric Allergy (SEICAP) has promoted a multicentre clinical trial in children between two and three years old who are allergic to milk [18], who did not yet have criteria for persistent allergy. The results obtained, with 90% of good evolution in the active group compared to only 23% in the control group (the possibility of tolerating was seven times higher in the active group, NNT of 1.45). Are stimulating to act precociously and in this way modify favorably the natural history of the disease. These experiences open new perspectives in the treatment of food allergy and are likely to change soon in childhood.

Another field in which advances are being made is in the knowledge of the changes that make an individual go from being allergic to tolerant. In natural tolerance, the moment in which this has been established is not known, but in immunotherapy the modifications can be measured exactly at the initial moment, in intermediate situations, at the moment when tolerance is reached and during follow-up. The changes with respect to IgE occur gradually and, although there is a decrease in the size of the skin test and in the specific IgE values between the beginning and the end of the treatment, these are manifested above all in the medium and long term (a 6 to 12 and a 18 months) and continue to decrease progressively in cases where monitoring has been carried out for several years. It is speculated that the specific IgE values represent only an epiphenomenon of other, more profound modifications. Recent studies describe changes in other immunological parameters such as interleukins or regulatory T cells [19,20], which are probably of greater transcendence and which are expected to be useful markers of evolution.

Current status of immunotherapy with food

The number of patients who have successfully completed these treatments at the present time is high, and it is estimated that in our country it greatly exceeds a thousand patients.

At present there are no unified data records. The procedures used are artisanal, the quantification of the allergen used is almost non-existent (only weight or weight /volume) and the methodology used is different in each series. Despite this, the efficiency obtained has triggered the demand for attention and the prospects for improvement with an early intervention can increase it even more.

Given that they are treatments carried out almost exclusively in children, the scientific groups of pediatric specialists must continue in the current line of leading and promoting homogeneous and well-designed multicentre studies, such as the one mentioned for milk and another one in progress for immunotherapy with egg, also coordinated by SEICAP, that allow to provide scientifically proven results that are useful and applicable to our daily practice.

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