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EDITORIAL

The slow progress in achieving an effective treatment for food allergy

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Food allergy is a significant health issue, as shown by a global prevalence of 3–10% when the diagnosis is established by appropriate allergy testing [1]. Though valid diagnostic procedures, including skin tests, *in vitro* tests, and, as gold standard, the double blind, placebo-controlled food challenge (DBPCFC), are available [2], an effective treatment of food allergy is still lacking. The elimination of the food(s) identified as responsible from the diet is of obvious importance, and it is able to obtain the loss of sensitization with development of negative tests when maintained for sufficiently long time, as known since the 1980s [3]. However, the achievement of the same outcome of prospective studies, where the patients are regularly monitored and educated in the need of avoiding the culprit food(s), in real life is challenging. The only treatment aimed at working on the cause of hypersensitivity is allergen immunotherapy (AIT), which has wide evidence of efficacy in respiratory allergy, with comparable results for subcutaneous and sublingual route of administration [4]. The possible application of subcutaneous immunotherapy (SCIT) for food allergy was evaluated in 1992 in patients with peanut allergy, but the finding of a clinical efficacy was counterbalanced by an unacceptable rate of systemic, and also severe, adverse reactions [5]. This prevented the further use of food SCIT, and the subsequent investigations were based on other routes of administration, including oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and, more recently, epicutaneous immunotherapy (EPIT) [6]. However, to date no definite evidence of efficacy is available for any of these treatments, and this does not make them accepted in guidelines and consensus documents on AIT. Table 1 summarizes the results of meta-analyses on OIT and SLIT for food allergy. Most meta-analyses addressed immunotherapy for single foods, in particular cow's milk [7–9] and peanut [10], while one included immunotherapy for several foods [11]. The first two meta-analyses were affected by imprecision of the estimates [7] and low quality of the evidence for efficacy [8]. The meta-analysis on OIT and SLIT for peanut allergy showed a significantly positive effect in actively treated patients than in controls, but the number of patients was small [10]. Two meta-analyses were based on large number of patients. Nurmatov et al. included 21 studies, 17 based on OIT and 4 on SLIT: a substantially lower risk of allergic reactions to the specific food in patients receiving orally

administered immunotherapy than in control patients was found, with a risk ratio of 0.21. However, the authors recommended that, 'given the paucity of evidence on longer-term safety, effectiveness, and cost-effectiveness, orally administered immunotherapy should not be used outside experimental conditions presently' [11]. The meta-analysis by Martorell Calatayud et al. included six randomized controlled trials on patients allergic to cow's milk. The results showed that OIT with cow's milk was effective for treatment of immunoglobulin (Ig)E-mediated allergy to such food, significantly more patients achieving tolerance with OIT than with an avoidance diet. Also, immunological effects were apparent, as shown by a decrease in cow's milk-specific IgE levels, though the difference with control patients was not significant [9]. Anyhow, the authors of both these analyses agreed on the need of additional larger, well-designed, and double-blind controlled studies. As far as safety and tolerability are concerned, a high rate of adverse effects was reported by Yeung et al, mostly mild and self-limited, but not infrequently requiring the use of epinephrine [8]. Concerning EPIT, promising data from experimental models, from trials performed with inhalant allergens, and from a pilot trial in children allergic to cow's milk are available [12]. However, such route of administration currently lacks demonstration of efficacy in controlled trials on food-allergic patients. New approaches for AIT include modification of the allergen molecules by chemical treatment or recombinant technology to lessen their reactivity with specific IgE, as well as the use of adjuvants allowing to decrease significantly the allergen doses [6]. Still, searching possible pitfalls in the trials performed thus far may help in understanding how to improve outcomes of AIT for food allergy.

1. Expert opinion

AIT for respiratory allergy was based for many decades only on the subcutaneous route. Its evidence of effectiveness was increasingly apparent with the improvement of quality of allergen extracts, but the concern of adverse reactions, that were rarely life-threatening and sometimes fatal, emerged as a drawback. In fact, SCIT is clearly dose-dependent according to both efficacy and safety, and the cutoffs of doses associated to an increased risk of reactions were identified

Table 1. Meta-analyses of controlled trials on immunotherapy for food allergy.

Authors, ref. number	Kind of IT	Food(s)	Number of patients and controls	Results	Limitations
Brozek et al. [7]	OIT	Cow's milk	116 patients, 114 controls	Increased likelihood of achieving full tolerance to milk (relative risk: 10.0)	Uncertainty of the effect of OIT due to serious imprecision of the estimates
Yeung et al. [8]	OIT	Cow's milk	106 patients, 90 controls	62% of patients able to tolerate 200 mL of milk vs. 8% of controls	Low quality of evidence for efficacy and high frequency of adverse effects
Nurmatov et al. [11]	OIT, SLIT	Cow's milk, hen's egg, fish, peanut, hazelnut, peach, and apple	484 patients, 327 controls	Lower risk of reactions to the specific foods (risk ratio: 0.21)	Paucity of evidence for long-term efficacy and safety
Sun et al. [10]	OIT, SLIT	Peanut	50 patients, 36 controls	Significantly positive effect by both treatments	A small number of patients was studied
Martorell Calatayud et al. [9]	OIT	Cow's milk	134 patients, 124 controls	Desensitization to milk 10.2 times more likely in OIT treated than in controls	Meta-analysis of safety was not performed due to differences in the presentation of data

IT: immunotherapy; OIT: oral immunotherapy; SLIT: sublingual immunotherapy.

and measured in microgram of major allergens [13]. The development of non-injective routes of AIT was driven by the safety issue, and the need was met by SLIT, which showed a good clinical efficacy while maintaining a suitable safety, with doses hundreds of times higher than those used for SCIT [14]. Instead, the allergen doses required to expect efficacy from OIT were too high to be cost-effective. Focusing on AIT for food allergy, it is conceivable that the allergen doses balancing the optimal efficacy and safety with SLIT and OIT are not yet identified, but it is also possible that such doses may be too high (as for OIT with inhalant allergens) to be cost-effective. Dose-finding trials are warranted to detect the cost-effective doses for the most important foods to be administered by oral or sublingual route. Concerning EPIT, based on the scant data available thus far, the doses to be administered are likely to be far lower, but more studies are needed to confirm this.

On the other hand, a reappraisal of SCIT with food allergens should be worthwhile if the approach of reducing the allergenicity and thus the risk of reactions will be used. The ongoing Food Allergy Specific Immunotherapy study is aimed at the development of safe and effective treatment of food allergies. Two important causes of allergy, i.e. fish and peach, will be evaluated by using the major allergen of fish, parvalbumin (Cyp c 1), and the major allergen of peach lipid transfer protein (Pru p 3). These allergens, following techniques such as site-directed mutagenesis and chemical modification to obtain hypoallergenic forms and evaluation in animal models, will be used for SCIT with alum-absorbed retard preparations in phase I/IIa and IIb randomized double-blind placebo-controlled clinical trials, with the DBPCFC as primary measure of efficacy [15]. In the phase I/IIa, 24 individuals, with a proportion active:placebo of 3:1, will be included to assess safety of SCIT. In the phase IIb, an estimated number of patients of 105 per trial (70 actively and 35 placebo treated) will be recruited. The efficacy in this phase will be measured by the intake of fish or peach assessed by DBPCFC compared to the pretreatment challenge.

It is to be hoped that this approach will be successful, paving the way to similar studies with other major food allergens and finally allowing to provide an effective treatment to food allergic patients.

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Declaration of interest

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