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POINT OF VIEW

Immunotherapy in the treatment of food allergy. Does it have a future?

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In recent years, food allergy has come to be seen as an emerging public health problem in the countries of our geographical setting. In addition, food allergy is the leading cause of anaphylaxis seen in Emergency Services, and unfortunately deaths as a result of such situations are still reported. At present, the only treatment option is strict avoidance of the causal food, and the administration of drugs such as adrenalin in the case of accidental reactions. Nevertheless, other more active approaches to the management of food allergy are becoming increasingly relevant.[1,2]

Conventional immunotherapy

Specific immunotherapy has been used for treating respiratory allergy since its early description by Noon in 1911.[3] At present, immunotherapy is acknowledged as being able to modify the host immune response to the causal allergen, and this immune modulating effect moreover persists once the treatment has been suspended.[4,5]

The use of immunotherapy in application to food allergy has been contemplated since the origin of such treatment. Indeed, as early as 1930, Freeman reported the first application of specific immunotherapy in a patient with fish allergy. Later, in the 1990s, two studies were published which proved vital for defining food immunotherapy as a probable effective treatment option, though with non-recommendable safety parameters.[7,8]

Separate mention must be made of the studies exploring the relationship between respiratory allergy and food allergy, and which gave rise to publications reporting clinical cases of patients with food allergy due to the known cross-reactivity between respiratory and food allergens.[9-12] However, the results of the clinical trials are ambiguous, and such therapy cannot therefore be considered as a treatment of cross-reactivity food allergy at the present time.[13-16]

As a result, conventional immunotherapy has been relegated in favour of studies based on new immune modulating strategies designed to reduce the risks seen with specific food immunotherapy. These novel strategies include immunotherapy with hypoallergens obtained by genetic engineering techniques, methods based on the stimulation of toll-like receptors; the use of adjuvants to promote Th1 response; the use of anti-IgE antibodies; sublingual immunotherapy; and even the use of traditional Chinese medicinal remedies for treating food allergy.

Sublingual immunotherapy for food allergy

Sublingual immunotherapy began to be used as an alternative to conventional immunotherapy in the 1980s. Since then, numerous double-blind, placebo-controlled studies and metaanalyses have confirmed its efficacy and safety in application to respiratory allergy.[17-21] A number of studies have also explored the action mechanism of sublingual immunotherapy. In this sense, the induction of tolerance is seen to be significantly mediated by both the interleukin-10 producing regulatory T lymphocytes and the Langerhans cells present in the oral mucosa, and which express high-affinity receptors for IgE.[23-25]

In the year 2005 a study was published which assessed the efficacy and safety of sublingual immunotherapy applied to food allergy, using hazelnut allergy as a study model.[26] This

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double-blind, placebo-controlled, randomised study included 23 patients with hazelnut allergy confirmed by provocation testing. The same technique was used to assess treatment efficacy. The duration of treatment was three months, preceded by an initiation week. Following treatment, the mean tolerated hazelnut dose increased from 2.29 g to 11.56 g, while the placebo group showed a non-significant increase from 3.49 g to 4.14 g. These efficacy data in turn were accompanied by very acceptable safety, and immunological evidence of efficacy such as increases in IgG_4 and IL-10.[26]

An interesting aspect of this study is that the patients spat out the extract after coming into contact with the sublingual mucosa. This fact, and the immunological parameters obtained, define sublingual immunotherapy as an optimum model for studying the mechanisms underlying food tolerance and the role of the dendritic cells and regulatory T lymphocytes in this process.

Another obvious advantage of sublingual immunotherapy is that its administration requires no use of health care resources. Further studies are of course needed to corroborate these results and to establish the possible long-term effects of such treatment.[27]

Other immunological treatments for food allergy

In recent years, different immunological approaches to the treatment of food allergy have been published. Such studies include the use of traditional Chinese medicine.[28,29] These studies began with the application of herbal mixtures used by such traditional practices. The studies have centred on the evaluation of which elements of these herbal mixtures are responsible for the therapeutic effect, and what their underlying mechanisms of action may be. Curiously, the efficacy in blocking anaphylactic responses in mice allergic to peanut and treated with these traditional herbs is associated to a Th2-Th1 regulatory response, in the same way as in conventional immunotherapy. Moreover, a marked reduction in specific IgE is observed and which persists for a long period of the life of the animal, after only a few weeks of treatment.[30] The purification of the natural products responsible for this therapeutic effect is one of the most promising options for the development of effective and safe treatment for food allergy. At present we are waiting for confirmatory studies in human models.

Another therapeutic alternative is the use of anti-IgE antibodies. Such treatment is indicated in patients with persistent moderate-severe asthma, and induces a reduction in serum IgE levels —inhibiting the immediate and delayed responses to allergens, and thus improving the symptoms of respiratory allergy.[31]

In the year 2003, a controlled study was published involving 84 patients with peanut allergy, treated with different doses of anti-IgE antibodies. After four months of treatment, an important reduction in the symptoms of the food allergy was recorded.[32] However, 25%of the patients showed no response to such treatment, which is moreover expensive and requires frequent and in-hospital administration. This therapy is being used as an adjuvant to conventional immunotherapy, with the purpose of lessening the serious adverse effects seen in some patients.[33] Such studies indicate that this association clearly reduces the adverse effects and moreover allows faster and more effective administration of the extracts.[31] In any case, no studies contemplating the use of anti-IgE antibodies and immunotherapy with food extracts have been published to date. This combination would not seem to be applicable in the case of sublingual immunotherapy use, due to the excellent safety performance reported by the latter treatment modality.

Other current studies on the treatment of food allergy include those based on genetic engineering techniques for obtaining mutant allergens with a view to generating hypoallergenic molecules amenable to use in immunotherapy.[34-41] The designing of molecules which maintain their antigenicity although with diminished allergenicity may give rise to promising safe and effective treatments for food allergy.[42,43] However, it must be taken into account that the immune response to foods is characterized by the implication of several allergens in one same food, i.e., a given food contains multiple allergens, and patients therefore may be sensitised to more than one of them. Another important factor which may complicate the choice of a candidate molecule is the geographical differences seen in allergen sensitisation patterns.[44,45] This aspect of such treatment may not be relevant in the case of sublingual immunotherapy, since the mechanism underlying the latter involves the intervention of IL-10 producing Langerhans cells expressing high-affinity IgE receptors. In this context, hypoallergenic molecules could obviate these receptors, thereby lessening the efficacy of sublingual immunotherapy.[23-25] It seems possible that preservation of the IgE epitopes may be relevant to their activation, presenting dendritic cells of the sublingual mucosa.[22,46]

Lastly, other strategies in the treatment of food allergy include studies based on the use of DNA fragments or immune stimulating sequences which lessen Th2-mediated responses. Such studies are presently based on animal models, with good results in terms of efficacy and safety.[47]

Conclusion

At present, the treatment of food allergy is based on strict avoidance of the causal food, and on the administration of drugs to deal with the clinical manifestations in the case of accidental reactions. Nevertheless, a range of promising new strategies are currently being studied, with acceptable results in terms of efficacy and safety. Thanks to its simple administration, sublingual immunotherapy may possibly play an important future role in the management of food allergy.

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