Oral lyophilisate and food immunotherapy: from research to clinical practice

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ABSTRACT

Thanks to its excellent safety profile, sublingual immunotherapy has served as a basis for launching two important lines of research in current allergology: sublingual immunotherapy with pharmaceutical registry (oral lyophilizates or tablets), and sublingual immunotherapy with food.

At present, clinical trials are being conducted which use rapid dissolution oral lyophilizates. The results of the clinical trials carried out in large patient groups and based on a double-blind methodological design have allowed pharmaceutical registry of this form of treatment, with the therapeutic indications of rhinitis and allergy to grasses. *Phleum* lyophilizate indicated for the treatment of rhinoconjunctivitis will be marketed in Spain in the coming months.

In parallel to development of the sublingual route, advances in our knowledge of pollen allergy and its relationship to plant food allergies have facilitated the conducting of studies involving sublingual immunotherapy for allergy to kiwifruit, hazelnut and peach – thus giving rise to promising future perspectives for affected patients.

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In the last two decades, and among the different forms of non-injected immunotherapy, the sublingual route has been shown to offer safe and effective treatment. In these 20 years, more than 100 studies have been published. Of these, 64 address treatment efficacy while 39 involve a double-blind methodological design, and a total of 6 systematic reviews have been generated to date[1,2].

Sublingual immunotherapy has been shown to be effective in reducing the symptoms and the need for medication among adults and children with allergic rhinitis caused by dust mites and pollen. Although the data relating to asthma have been positive in the clinical trials conducted to date, efficacy has been discrete. The indications of sublingual immunotherapy in application to allergy to animal epithelia, fungi, latex and hymenopter venom remain to be established.

Recently, Di Rienzo et al. conducted a prospective follow-up study of sublingual immunotherapy for dust mite allergies in children. Treatment proved effective over the long term, and was able to prevent the appearance of asthma – although the study design does not seem to have been the most appropriate. However, the appearance of new sensitisations was found to be identical in the active treatment and control groups[3].

There are no comparative studies of sublingual immunotherapy versus drugs, although comparisons have been made versus subcutaneous immunotherapy with grasses[4] and – in a methodologically correct trial – also with birch extract[5].

As regards treatment safety, examined in large patient series, the results are excellent and systemic reactions have been practically inexistent – with the exception of some specific extract such as latex[6].

The questions that still require answers are the following: effective dose, the optimum starting regimen, and the ideal duration of treatment, as well as long-term efficacy, the collection of further data in paediatric patients, safety in high risk groups (e.g., asthma and polysensitised patients), and possibly also cost-benefit assessments.

From our perspective, and thanks to its excellent safety profile, sublingual immunotherapy has served as a basis for launching two important lines of research in current allergology: sublingual immunotherapy with pharmaceutical registry (oral lyophilizates or tablets), and sublingual immunotherapy with food.

ORAL LYOPHILIZATES

Clinical trials are currently underway with fast dissolving oral lyophilizates developed by two different companies. In turn, the results of clinical trials carried out in large patient groups and based on a double-blind methodological design have allowed pharmaceutical registry of this form of treatment, with the therapeutic indications of rhinitis and allergy to grasses. These *Phleum* or *5 mix grasses* lyophilizates indicated for the treatment of rhinoconjunctivitis will be marketed in Spain in the coming months.

A fundamental trial has been a multicentre survey conducted in Europe and Canada, involving 855 patients with allergy to pollen. This trial involved a double-blind and placebo controlled dose-response design with three concentrations of rapid dissolving tablets. All patients were adults with a diagnosis of rhinoconjunctivitis. The treatment was carried out without an initial dose increasing phase, and involving a single daily dose during a period of four months, pre- and co-seasonal. An evaluation was made of the symptoms; adverse reactions; need for medication; and quality of life. The treatment was well tolerated, and no serious adverse reactions or cases of anaphylactic shock were recorded. The benefits obtained were dose-related. Treatment reduced the symptoms and need for medication, and the patients in the active drug group showed improvement in quality of life[7].

Publication of the efficacy results of the clinical trials conducted by the other company, and the results in paediatric populations present a similar picture[8,9].

Publications are still pending of the work carried out with dust mites and for the therapeutic indication of asthma. In the coming years, the registry-approval of this treatment modality is to be expected, with the therapeutic indications of rhinitis and allergy to grasses and dust mites in both adults and in children.

FOOD IMMUNOTHERAPY

While specific immunotherapy has been commonly used for almost a century as treatment for respiratory allergies and hymenopter venom allergic processes, and although parallel attempts have been made to apply such therapy to food allergies, the poor results obtained and the high incidence of adverse effects have not allowed its routine use in clinical practice to date. The fact that patients with food allergy present monosensitisation, and that allergen avoidance in such cases is usually effective, possibly explains why immunotherapy has not been developed as a treatment alternative in food allergy. However, some patients suffer serious symptoms, while others have avoidance problems (as in cases of plant foods), and in general all of them experience a reduction in quality of life because of the life-long need to avoid certain foods. Therefore, and from our perspective, the search for treatment alternatives capable of attenuating or suppressing serious reactions and improving patient quality of life is clearly justified. There have been reports where this treatment modality has been used on a compassionate basis and in patients with extremely severe food allergy – with positive results.

The most important double-blind subcutaneous immunotherapy study with peanut extract was conducted in 1992. The death of a patient, resulting from error, stopped the inclusion of new patients. Nevertheless, the results obtained from the limited number of valuable subjects have been published, and the final conclusions confirm that the high rate of systemic reactions speaks against the routine use of this type of treatment[9,10].

In parallel to development of the sublingual route, advances in our knowledge of pollen allergy and its relationship to plant food allergies have facilitated the conduction of studies involving sublingual immunotherapy for allergy to kiwifruit, hazelnut and peach (data *in press*) – thus giving rise to promising future perspectives for affected patients[11-15].

The good treatment tolerance recorded in these surveys, and the finding in different studies that pollen immunotherapy eliminates or reduces sensitivity to related fruits, have generated renewed impulse for food immunotherapy.

In the case of peach, for example, the treatment significantly reduces patient reactivity to the fruit – postponing the local symptoms onset dose and re-

ducing systemic reactions in response to high doses. Patient desensitisation is also detectable at skin and immune level. Moreover, the treatment is safe, without serious adverse reactions, and with systemic reactions similar to those seen with placebo. The great majority of patients only experience local discomfort such as oral itching.

Will immunotherapy be prescribed in tablets, and will this treatment modality be used in application to food allergies? We believe that the answer is yes, and that such application will become a fact in the very near future.

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