

SUBLINGUAL IMMUNOTHERAPY: FROM SAFETY TO MECHANISM OF ACTION

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SUMMARY: Allergen specific immunotherapy is an important option for the treatment of respiratory allergy and its clinical efficacy has been clearly demonstrated by several studies. However, the injective route of administration and the possibility of severe side effects has limited its use in children and led to the introduction of new forms of administration. Sublingual immunotherapy (SLIT) has proven to be an effective and safe treatment for respiratory allergy. However, its mechanism of action is still debated. Pharmacokinetic studies showed that, differently from nasal mucosa, allergen extracts administered by SLIT are not immediately adsorbed but are long retained before being drained to local lymph nodes. This difference may be responsible of the absence of severe side effects and instead of short-lasting local symptoms. Studies by biopsies of the oral mucosa should greatly help in defining the presence and the role of cells involved in the mechanisms of oral tolerance.

Key-words: Sublingual immunotherapy - Oral mucosa - Safety - Tolerance.

INTRODUCTION

Allergen specific immunotherapy (SIT) is an important option for the treatment of respiratory allergy, whose clinical efficacy was clearly demonstrated in the last 50 years and fully validated by WHO in 1998 (1).

Differently from pharmaceutical approach, which can only be considered to prevent and control symptoms, SIT is the only therapeutic choice which can modify natural history of allergic disease.

Alternative ways of administration to the classical form of subcutaneous immunotherapy (SCIT), in order to minimize side-effects, were studied in the second half of '80, since sublingual immunotherapy (SLIT) was introduced in 1986 (2). After the first studies with low-dose SLIT, in the latest years several double-blind placebo controlled (DBPC) studies were performed, increasing our knowledge about efficacy, safety, and dose comparison with a wide diffusion of SLIT in Europe (3). The efficacy of SLIT was recently confirmed by a meta-analysis considering 22 DBPC studies (4), and its safety demonstrated also in children, using cumulative doses up to 500 times higher than those administered with SCIT (5, 6).

The main study comparing safety and efficacy of SIT and SLIT (7), performed in patients with birch pollen

allergic rhinitis, showed a similar clinical efficacy but with side-effects significantly higher and more important in SIT, and focused the attention to the different mechanisms of action of these forms of immunotherapy. Allergen extracts were initially considered passively crossing the oral mucosa and thus eliciting systemic reactions, but recent studies of pharmacokinetics showed that there is no allergen absorption in the oral mucosa. This data is confirmed by the presence of local and not systemic typical side effects in SLIT, namely in mouth and in gastrointestinal tract. However, allergen extracts are able to determine immunological modifications such as the blunting of seasonal rise of specific IgE in the target organ, as demonstrated in the nasal mucosa of grass allergic subjects treated with high dose SLIT (8).

It is important to note that a role for intestinal absorption in inducing tolerance is unlikely, since oral immunotherapy, in which allergen extracts are swallowed without any contact with the oral mucosa, failed to demonstrate, despite some positive results with particular preparations (9), a clinical efficacy (3), this data stressing the importance of local mucosa in the evident reduction of sensitivity which takes place in subjects treated with SLIT.

However, the real mechanism involved in oral tolerance is still not demonstrated although Langerhans-like dendritic cells (10) and T regulatory lymphocytes seem to play a pivotal role in this complex mechanisms, and their study offers new perspectives in the investigation of the immunotolerance mechanisms.

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PHARMACOKINETICS OF SLIT

The path of the allergen after contacting the sublingual mucosa may suggest the mechanism of sublingual immunotherapy. Recent investigations by Canonica's group studied the pharmacokinetics of the allergens using radiolabelled materials, which included native and modified allergens, and compared oral and nasal administration (11-13).

The results of such studies showed that the sublingually administered allergen (namely the major allergen from *Parietaria judaica* Par j 1) was not absorbed through the oral mucosa, but was retained at mucosal level for up to 20 hours, and that after swallowing a gastrointestinal absorption occurred but that the plasma radioactivity (peaking at 1.5-3 hours) was due to free radioiodine and small peptides but not to native allergen.

On the contrary, the nasal administration of Par j 1 in *Parietaria* allergic patients is associated to a kinetics with rapid clearance from the nasal mucosa, little local persistence in the pharynx, and increase in plasma radioactivity after swallowing.

IMMUNOLOGICAL MECHANISMS IN THE ORAL MUCOSA

The contact of the oral mucosa with the allergen administered by SLIT leads to activation of dendritic cells, which phagocytate the allergen in the most superficial layers and transport it to the draining lymph nodes. Once migrated in the lymph nodes, dendritic cells express co-stimulatory molecules and interact with local CD8 and CD4 T cells (14).

The immunologic effects on T cells might be related to two distinct mechanisms able to account for the clinical effectiveness of SLIT.

A first mechanism may be responsible of the short-term efficacy of SLIT observed with ultra-rush or co-seasonal treatment in patients with pollen allergy (15, 16): as suggested by Bousquet, down regulation of mast cells is more efficient with the higher allergen doses administered in a short time and results in a lower reactivity during the pollen season (16).

A second mechanism involves Treg activation, which is likely to be related to the long-lasting effects, characteristic of prolonged immunotherapy, observed also with SLIT (17). In particular, the differentiation in Treg of naive T cells is stimulated by the application of soluble antigens to the mucosae, with the involvement of dendritic cells (18, 19). Antigen specific Treg have a suppressive effect on both Th1 and Th2 response and, at least for the type 1 cells (Treg1), suppress the immune response with an increased production of IL-10 (20). Recently, a first report on this

issue showed that patients treated with prolonged SLIT with house dust mite extract had a significant production of IL-10, which was not observed in untreated patients with allergic rhinitis to mites (21). Other important aspects are the anatomical and immunological peculiarities of oral mucosa, when compared with bronchial and nasal mucosa, with a low number of oral mast cells, eosinophils and basophils, which is likely to underlie the absence of severe side effects to administration of high allergen doses (8, 22).

The hyporeactivity of the oral mucosa was recently confirmed by a study which used recombinant allergens and demonstrated that subjects with oral allergy syndrome tolerate sublingual administration of Bet v1 and Phl p1 at much higher doses than those needed to elicit allergic responses in the skin and in the nose (23). In spite of this, some subjects actually develop oral reactions to allergen extracts administered with SLIT: in a recent compliance study, about 6% of SLIT-treated withdrew the therapy because of local reactions (24). Investigating the mechanism underlying the development of such reactions it is a need to meet in the future.

CONCLUSIONS

Among the different routes of allergen immunotherapy, the sublingual route, which joins clinical efficacy to a high safety profile, is currently increasingly used as a valid option for treating respiratory allergy, and offers promising perspectives of development.

In fact, the effectiveness of SLIT could be further improved by a better knowledge on the mechanisms of mucosal tolerance leading to the introduction of materials and doses optimally fitting with both the pharmacokinetics and the immunizing capacity of the sublingual route. The limited local symptoms after allergen contact and the absence of delayed and severe systemic side-effects suggest the presence of immunological, and maybe anatomical, differences between oral mucosa and the other sites of allergen contact (i.e nasal and bronchial mucosa).

Indeed, in order to achieve a better understanding of the mechanism of oral tolerance in SLIT, bioptic samples and cytokine studies are needed to clearly define which cells are involved in allergen presentation to T cells and in the cascade of allergic inflammation.

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