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Sublingual Allergen Immunotherapy: the role of Th1 response

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Abstract

Allergy Immunotherapy can be mainly administered either through the subcutaneous or sublingual route. Sublingual immunotherapy has been investigated in allergic patients for the last twenty years and is considered as a valid noninvasive alternative to subcutaneous therapy.

In allergic rhinitis patients presents with mucosal inflammation, characterized by a Th2 polarization. The rational of SLIT is that oral administration of high-doses of allergen may reduce and prevent IgE responses.

SLIT seems to be able to shift allergen-specific CD4⁺ T-cells responses from Th2 to Th1: in fact, immunological changes associated with immunotherapy include diminution of Th2 cytokines (such as IL-4, IL-5 and IL-13) and increase in Th1 ones (IFN-gamma, IL-10, TGF-beta and IL-12).

Therefore, both IL-10 and TGF- beta lower the release of pro-inflammatory mediators and inhibit the production of Th2 cytokines. The role of IL-10 as an early marker of successful immunotherapy has been proposed, but, so far, no predictive marker of clinical response has been validated.

SLIT is a safe and effective route of administration of allergen extracts in allergic patients. However, its mechanism of action is still not fully understood, as there are few data concerning the immunologic changes induced by SLIT.

Keywords: Allergen Immunotherapy, AIT, Sublingual Immunotherapy, Subcutaneous Immunotherapy, T-Reg, Th1, IL-10

One hundred years after the pioneer studies by Noon and Freeman, allergen immunotherapy (AIT) is currently the only curative treatment for type I allergies (1). Immunotherapy has been traditionally administered by the subcutaneous route, but sublingual administration has also become a viable and interesting option (2). Such an option seems to be preferred in Europe, while Sub-Cutaneous Immunotherapy (SCIT) is still the main option in the United States.

Sublingual Immunotherapy (SLIT) was investigated in allergic patients almost twenty years ago and is now established as a valid noninvasive alternative to subcutaneous immunization to treat type I respiratory allergies (1). Sublingual uptake and processing of allergens have a number of specific features.

In most SLIT regimens, the allergen preparation is kept under the tongue for a few minutes and then swallowed or, in a small proportion of regimens, spat out (3).

Contraindications for SLIT are mainly same as for subcutaneous immunotherapy (SCIT), as they include lack of compliance, pregnancy, uncontrolled asthma, immunodeficiency, and autoimmune diseases (2).

For SLIT additionally, oral mucosal diseases and oral surgery might be temporary contraindications in those cases in which immunotherapy might irritate the mucosa (2). The immediate benefit of SLIT is that patients are no longer reluctant to start immunotherapy treatment and allergen immunotherapy prescriptions have increased to treat patients with allergic rhinitis and asthma (2). Moreover, there is clear evidence that AIT is effective in patients suffering from AR and asthma as already stated in the first WHO position paper, dealing with such a treatment (4).

Allergic Rhinitis (AR) represents the most common immune-mediated disorder, and its prevalence is increasing worldwide (5). Multiple studies further compiled in meta-analyses have demonstrated the efficacy of sublingual drops in adult and pediatric patients with allergic rhinitis, with a reduction in both symptoms and need for symptomatic medication (1). The disease is characterized by a certain degree of mucosal inflammation, with mast cell and eosinophil activation.

This inflammatory reaction switch the cytokines pattern towards an increased production of interleukin (IL)-4 by Th2 cells, with concomitant reduction of interferon (IFN)-gamma by Th1 cells and inhibition of their production (6). Th2-derived cytokines, such as IL-4 and IL-13, are the primary pathogenic factors in inducing, maintaining, and amplifying the allergic inflammation.

IL-4 and IL-13 orchestrate the inflammation promoting IgE synthesis, up-regulating adhesion molecules selective for eosinophil recruitment, and causing increased mucus production and airway hyper-reactivity (7). On the other hand, there is an increasing evidence that Th1-related cytokines, such as IFN-gamma and IL12, may suppress and counteract this Th2 response and vice-versa, as there is functional dichotomy between Th1 and Th2 cells (8).

When treating a patient presenting with AR, patient education and maximal allergen avoidance are the two cornerstones of therapy. General practitioners commonly prescribe nasal steroids, anti-histamines, leukotrien receptor antagonists, and symptomatic drugs. Specialists might prescribe Allergen Immunotherapy (AIT), which aims to reduce allergic symptoms and need for symptomatic medication (9-11).

AIT is classically based on the subcutaneous administration of allergen extracts (SCIT), but as this route of administration showed some risks of severe adverse reactions, alternative routes of immunotherapy, including oral, sublingual, nasal, and bronchial have been investigated and developed (12). The rationale of SLIT is that oral administration of high-dose allergen may reduce and prevent IgE responses. In contrast to SCIT, SLIT appears to elicit mucosal IgA responses, which may contribute significantly to tolerance induction (3). One obvious difference between SCIT and SLIT relates to the allergen

doses administered. SLIT requires at least 50–100 times more allergen than SCIT to achieve a similar level of efficacy (3).

Mice oral immune system, shows three subsets of oral dendritic cells (DCs), including Langerhans cells (in the mucosa), myeloid DCs (along the *lamina propria*), and plasmacytoid DCs (in the submucosal tissues). In humans, Langerhans cells (LCs) have similarly been described in the mucosa itself, whereas other DCs are less abundant (1).

All these different types of DCs seem to be tolerogenic, since capable of producing both IL-10 and IL-12 cytokines and therefore to lead naïve CD4⁺ cells to a Th1/T Reg phenotype (1).

Only few pro-inflammatory cells are found in oral tissues, mostly in the muscular layers, where allergens are more likely to be captured by tolerogenic dendritic cells in the upper layers of oral tissues prior to reaching proinflammatory mast cells, thus explaining the excellent safety profile of the sublingual route, with virtually no risk of severe systemic reactions when compared with the subcutaneous route (1).

In fact, SLIT safety and efficacy have been highlighted in the latest WHO position paper of 2009 (13), in the EAAACI document of 2010 (14), in several ARIA-WHO document, the latest being published in 2010 (15), and by several other consensus; moreover, they have been evidenced by two meta-analyses focusing on patients with AR and asthma (16, 17). In contrast, the subcutaneous injection route is associated with a greater risk of direct contact between the allergen and circulating pro-inflammatory basophils and Th2 lymphocytes (3). Additionally, the allergen is likely to be captured by myeloid or plasmacytoid DCs whose effector immune responses are associated with the release of pro-inflammatory mediators (3).

The exact mechanism of action of SIT is not completely understood (18), but several studies have suggested similar immunological changes with SCIT (19). Immunological changes associated with SCIT include induction of T Reg cells, increase in allergen-specific IgG4, IFN-gamma, IL-10, TGF-beta and IL-12, with down-regulation of the TH-2 response and decrease in IL-4, IL-5 and IL-13 (19). In general, AIT seems to generate regulatory T cells secreting both IL-10 and TGF-beta and specifically to suppress allergen-induced responses (20).

In particular, SLIT seems to be able to shift allergen-specific CD4⁺ T-cells responses from Th2 to Th1, with the stimulation of IFN-gamma-producing T lymphocytes (1). SLIT also induces type 1 regulatory T cells (Tr1), which produce high levels of IL-10 and/or of TGF-beta, known to decrease IgE production and to enhance IgG4 and IgA production, respectively (1). In addition, both IL-10 and TGF- beta lower the release of pro-inflammatory mediators and inhibit the production of Th2 cytokines (1). Moreover, specifically for SLIT, it has recently been evidenced the appearance of an induction of allergen-specific tolerance, as documented by restored allergen-specific IL-10 and IFN-gamma production (21).

Previously, it has been indicated that a rapid increase in IL-10 production, such as after the maintenance dose was reached, is crucial for the beneficial outcome of the SCIT in AR patients (22). Therefore, the role of IL-10 as an early marker of successful immunotherapy has been proposed, but there is not a general agreement on this subject and no predictive markers of clinical response are currently available (23).

AIT is highly effective in the treatment of AR, as it is the only treatment which leads to a prolonged tolerance against previously disease-causing allergens, resulting from the restoration of normal immunity (24). SLIT is a safe and effective route of administration of allergen extracts in allergic patients. However, its mechanism of action is still not fully understood, as there are few data concerning the immunologic changes induced by SLIT. Moreover, so far, many people initiate SLIT but there is still no prognostic parameter capable of identifying responders, as a certain percentage of them do not show clinical benefits.

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