

The Effect of Immunotherapy in Allergic Respiratory Diseases: Reappraisal of Current Knowledge

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Abstract

Allergic rhino-conjunctivitis and asthma are induced by sensitization to one or more allergens in susceptible individuals. Specific immunotherapy (SIT) is indicated in allergic diseases, because it modulates the immune response inducing peripheral T-cell tolerance and activation of regulatory T-cells. On this basis, SIT is considered the only therapeutic approach that can modify the natural history of the allergic diseases. The development of engineered-allergen has contributed to reduce the allergenicity thus preventing the risk of side effects. The monomeric allergoids, with structural conformation and molecular size that facilitate the mucosal absorption, carry a lower risk for side effects compared to the administration of native allergens, maintaining the immunological stimulation. The efficacy of SIT, administered percutaneously (SCIT) or sublingual (SLIT), has been largely demonstrated in rhino-conjunctivitis; moreover, clinical trials have also demonstrated the efficacy of immunotherapy in allergic asthma. A therapeutic effect on asthma control has been shown in asthmatic subjects allergic to house dust mites, parietaria or grass pollen. An important and intriguing aspect of immunotherapy, not shared with the standard pharmacological treatments, is the long-lasting effect after discontinuation. In this respect, several SLIT studies in adults and children have clearly shown that the beneficial effects are maintained for up to 6 years after discontinuation of immunotherapy. The current review describes the main indications for SIT, and discusses its efficacy and safety in allergic rhino-conjunctivitis and asthma.

Keywords Rhinitis; Asthma; Vaccine; Allergen

Introduction

Allergic rhino-conjunctivitis and asthma are caused by sensitization to one or more allergens in susceptible individuals. Specific immunotherapy (SIT) is indicated in IgE-dependent allergy and represents a potentially curative treatment approach in allergic diseases. The WHO Position Paper on Allergen Immunotherapy, published in 1998 [1], proposes SIT as the only treatment that affects the natural course of allergic diseases, potentially preventing (or delaying) the development of asthma in patients with allergic rhinitis. The traditional subcutaneous immunotherapy (SCIT) has been largely demonstrated to be effective in inducing tolerance in individuals with allergic respiratory diseases. However, the risk of severe adverse events (SAE), partly related to technical or human errors, is not of little importance [2,3].

The practice of administering sublingual immunotherapy (SLIT) for respiratory allergy, introduced for the first time in the mid-eighties [4] is gaining increasing diffusion worldwide based on the proved clinical efficacy and safety both in adult and in pediatric individuals with allergic rhino-conjunctivitis and/or asthma sensitized to seasonal or perennial allergens [5-8]. However, data from randomized trials comparing SLIT with SCIT are scarce, and do not seem to demonstrate significant differences between the two treatments. Similarly, indirect comparison did not provide conclusive results [9], although a more prominent effect of SCIT was found with regard to grass pollen [10]. Preliminary studies suggest that SLIT may have a role in other allergic conditions such as atopic dermatitis, food, latex and venom allergy [11].

The Immunological Mechanism of Specific Immunotherapy (SIT)

Immune responses in allergic subjects are characterized by impaired inhibitory function of allergen specific T-regulatory cells and aberrant activity of T helper type 2 (Th2) cells. The key cytokines responsible for the allergic response include IL-4, IL-13, and IL-5; these interleukins stimulate Th2 differentiation of T-naive cells and IgE production by B lymphocytes, which are responsible for the occurrence of symptoms after antigen re-exposure. Peripheral induction of T cell tolerance by allergen-specific regulatory Th1 cells is vital to healthy immune responses to allergens. The objective of SIT is the induction of immune tolerance to allergens, through changes in memory-type and allergen-specific T and B cell responses and up-regulation of mast cell and basophil activation thresholds. The shift in the balance between allergen specific Th2 and T-regulatory cells is central to either development of allergen tolerance or allergic status or even the recovery from allergic disease [12-14]. The T-regulatory cell stimulation by allergen causes the increased production of IL-10 and TGF- β .

IL-10 is a significant inhibitor of the allergic response, inhibiting the production, recruitment and survival of eosinophils and reducing the number of mast cells. Furthermore, IL-10 reduces the activation of allergen-specific Th2 cells, and induces suppression of IgE. In addition, IL-10 promotes the synthesis of IgG4, which is a non-inflammatory isotype that protects from allergic reaction by preventing the activation of mast cells and basophils. TGF- β is an important suppressive cytokine that is essential for the maintenance of immunologic self-tolerance; it modulates the conversion of naive

CD4+ T cells to Treg cells, which is required for both expansion in number and suppressive capacity of Treg cells.

The aim of allergen SIT is to induce the peripheral T cell tolerance, modulate the thresholds for mast cell and basophil activation and decrease IgE-mediated histamine release. Different mechanisms are involved in rendering mast cells and basophils unresponsive to allergens even if these cells are "sensitized" by specific IgE bound to their receptor.

The described shift in immunoglobulin isotype production cannot explain the therapeutic effect of SIT. In general, the decrease in serum IgE appears much later than clinical tolerance, which occurs relatively early during the course of SIT and does not correlate with the magnitude of clinical improvement after treatment. After the first administration of SIT, a very early decrease in the susceptibility of basophils to degranulation and systemic anaphylaxis can be observed [15]. Histamine is one of the main mediators released upon triggering of basophils and mast cells, and it exerts its functions through histamine receptors (HRs) [16,17]. The release of mediators from mast cells and basophils at low levels, below the "normal" threshold of systemic anaphylaxis is probably taking place during SIT [18,19]. Thus, successful hyposensitization is associated with the altered magnitude of mediator release from the effector cells [18].

Efforts to develop a safer and more effective SLIT have led to the development of allergoids, recombinant allergens and formulations with adjuvants and substances targeting antigens to dendritic cells that play a crucial role in initiating the immune responses. The chemical modification of native allergens to reduce their IgE-binding activity, as shown by *in vitro* (immune-inhibition assays, basophil activation, and basophil mediator release) and *in vivo* techniques (skin testing and nasal provocation), produces hypoallergenic preparations that retain the T-cell reactivity (antigenicity), as well as the ability to induce allergen-specific IgG antibody response (immunogenicity), which are essential for the clinical effects.

The chemical modification traditionally obtained by reaction with glutaraldehyde or formaldehyde yields polymeric allergoids, with high molecular weight, suitable for injective route only. The monomeric allergoid for sublingual administration reduces the interaction with specific IgE. This leads to the enhanced tolerability of the monomeric allergoid and the potential of reducing the dose of allergen that is necessary to maintain the "therapeutic" activity. The monomeric (carbamylated) allergoids provide the structural conformation and molecular size needed to allow mucosal absorption. Preparations based on carbamylated allergoids currently represent the only chemically modified allergens suitable for sublingual administration, inducing the tolerance induction through the stimulation of the oral mucosa-associated and gut-associated immune system with systemic absorption [11].

Safety of SIT

A large number of post-marketing studies documented the optimal safety profile, with incidence of side effects lower than 10% of treated patients with monomeric allergoids [20-22]. This high safety, in combination with high efficacy, was demonstrated in different induction (two up-dosing, one no-up-dosing) phase schedules [23] in subjects with rhino-conjunctivitis with or without asthma due to sensitization to perennial and seasonal allergens. Conversely, SLIT with native (i.e. not allergoid) allergens without up-dosing has been submitted to clinical trials to evaluate efficacy and safety, showing

adverse events (mainly local) in a large percentage of treated patients (67%) [10,24]. This phenomenon is probably due to the nature of the active substance (native allergen), which maintains the ability to react with allergen-specific IgE antibodies, and consistently increases the serum concentration of these antibodies (approximately five-fold).

The potential risk of *de novo* sensitization to epitopes present in the vaccine theoretically exists. Some cases of neo-sensitizations have been described with SCIT; nevertheless, the risk is expected to be much lower when the allergen is delivered in an immune environment that increases tolerance induction such as the oral mucosa, as recently observed for SLIT to grass pollen and house dust mite [25,26]

Efficacy of SIT in Allergic Rhino-Conjunctivitis

SIT for respiratory allergy is considered complementary to the pharmacological approach for the purpose of reducing symptoms and the need for rescue medications [27]. SLIT is mainly indicated in rhino-conjunctivitis; in more than 60 positive studies (two thirds of them in dust mites and grass allergy), the magnitude of clinical effects ranged from 10 to 45% over placebo [28].

In 1998, Passalacqua and collaborators [29] demonstrated the efficacy of SLIT with monomeric allergoids derived from *Dermatophagoides* in patients with rhino-conjunctivitis compared with placebo group, in terms of reduction of symptoms and drug consumption after the first year of administration ($p < 0.05$), which was even greater after the second year ($p < 0.01$). In subjects affected by rhino-conjunctivitis treated with SLIT, a clear reduction in the allergic inflammation parameters (neutrophils, eosinophils, ICAM-1) evaluated after one and two years was demonstrated ($p < 0.001$). A reduction in the eosinophil cationic protein (ECP) in the serum was also observed after both the first ($p < 0.01$) and the second year ($p < 0.04$) of immunotherapy. No adverse events were observed. The same authors [30] confirmed the effectiveness of SLIT with *Dermatophagoides* in terms of reduction of nasal obstruction, use of symptomatic medication, number of extra visits and improvement in the health-related quality of life parameters.

Efficacy of SIT in Allergic Asthma

Recent systematic review articles comparing the efficacy and safety of SLIT with those of other treatments for rhinitis and asthma have shown the superiority of immunotherapy [31,32]. However, asthma symptoms rarely represent the primary outcome [28]. Recently, a therapeutic effect on asthma control was demonstrated in asthmatic subjects allergic to house dust mites. Compared to placebo, the SLIT decreased the need of inhaled corticosteroids after one year of daily treatment [33]. A recent study investigated whether SLIT with chemically modified allergen extract provided an additional advantage in real-life settings and in a relatively long-term period, achieving the control of mild persistent asthmatic symptoms related to birch pollen [34]. Given the high tolerability of SLIT, its use in more severe forms of allergic asthma could be proposed [1]; this however needs to be addressed in specifically designed studies.

SLIT in bronchial asthma allergic to *dermatophagoides pteronyssinus* demonstrated to reduce the rate and severity of asthmatic attacks ($p < 0.001$) and to improve lung function, by means of peak expiratory flow ($p < 0.001$) [35]. A multicenter, randomized, open-label study was conducted in children suffering from asthma with or without rhinoconjunctivitis and monosensitized to *dermatophagoides*. Subjects were divided in two groups, one treated with SLIT for

dermatophagoides formulated in tablets containing the monomeric allergoid and the second with delayed-release SCIT with extracts [36]. The study confirmed the safety and efficacy of both treatments with SLIT being more indicated in young children who often do not accept the frequent injections required by SCIT. The efficacy of SLIT for graminaceae in adults with rhino-conjunctivitis and asthma has also been proven in terms of reduction in both global and nasal symptoms compared to volunteers treated with placebo [37].

Patients treated with active drug also used less medications, particularly bronchodilators. These differences could already be seen after the first year of treatment, and were even more pronounced after the second year. These results were replicated in asthmatic children allergic to grass pollen [38]. Indeed, treatment with a monomeric allergoid incorporated into small tablets (\varnothing 7 mm) in doses of 25, 100, 300 and 1,000 UA/tablet was responsible for significantly fewer respiratory symptoms compared to the placebo group in the first year. During the second year, the active treatment group also showed a reduction in the drug consumption score. Finally, a significant reduction ($p < 0.01$) in bronchial reactivity together with a significant reduction in rhinitic ($p < 0.001$) and asthmatic ($p < 0.001$) symptoms was observed in patients allergic to grass pollen treated with SIT compared to those receiving only symptomatic drugs [39].

In the above-cited study, the group treated with SIT demonstrated a significantly lower use of symptomatic drugs ($p < 0.001$). These findings were confirmed by La Grutta and colleagues in subjects with asthma (with or without rhinitis) who were allergic to house dust mite and *Parietaria* ($p < 0.0005$) [40].

The Long-Lasting Effect after SIT Discontinuation

An important and intriguing aspect of immunotherapy, which is missing in conventional pharmacological treatments, is the long-lasting beneficial effect after discontinuation. Several SLIT studies in adults and children show that the beneficial effects are maintained for up to 6 years after discontinuation of SLIT [41-45]. A study conducted between 1992 and 2005 evaluated the long-lasting effects of SLIT for house dust mites in allergic rhinitis with airway hyperresponsiveness [46].

Patients had been treated with the monomeric allergoid in tablets, with a standard induction phase of 14 weeks, and divided into four groups according to the duration of treatment. All patients underwent a comprehensive clinical (symptom/drug scores) and functional (lung volumes, airway hyperresponsiveness) evaluation at baseline and approximately every 2 years for the duration of the study. The main finding was the reduction in the symptom/drug scores that persisted for 8-9 years after the completion of SLIT, when this was administered for 4 years ($p < 0.001$ versus baseline); shorter treatments led to less persistent effects over time, although statistically significant ($p < 0.05$ versus baseline). A reduction in the degree of airway hyperresponsiveness was also observed 6-7 years after the completion of treatment ($p < 0.001$).

Conclusions

Desensitization represents a potentially curative and specific approach to allergies [37]. Although SLIT and SCIT are the two main routes of administration, SLIT seems to be the more safe and favorable route of both. Several large-scaled, randomized, double-blinded, placebo-controlled trials demonstrated the long lasting and disease-modifying effects of SLIT [47-51]. The main indication for SIT

remains allergic rhino-conjunctivitis. However, a body of evidence confirms the effectiveness of SIT in allergic asthmatics in reducing airway hyperresponsiveness, symptoms and use of rescue medications. The advantages offered by SIT become evident in the long-term period, especially when compared to pharmacotherapy. The ability of SIT to modify the inflammatory response to allergens makes it the only therapeutic approach that can modify the natural history of the allergic diseases.

There is a general agreement that an appropriate use of SIT, based mainly on the techniques of molecular analysis of the antigens, may represent the complementary approach to pharmacological treatment for the optimal management of respiratory allergies. We indicate that this treatment should be primarily proposed to individuals with allergic rhino-conjunctivitis who are sensitized to a single allergen, not only to reduce the symptoms and the use of rescue medications, but also to prevent the development of bronchial asthma. The different clinical responses to treatment and in the immunological changes require further studies to identify the candidate patients to SLIT, as well as the biomarkers capable of predicting short- and long-term efficacy on the other hand.

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