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Sublingual immunotherapy in allergic rhinitis

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Current treatment options for allergic rhinitis (AR) include allergen avoidance and environmental control, pharmacotherapy, nasal surgery and immunotherapy. Among these, immunotherapy is the only therapeutic option that modifies fundamental immunologic mechanism by inducing desensitization. Specific allergen immunotherapy has been used for 1 century since 1911 and subcutaneous immunotherapy (SCIT) has been demonstrated to be effective in asthma and AR. However, SCIT has several disadvantages such as inconvenience, invasiveness and potentially severe systemic reactions. Thus, sublingual immunotherapy (SLIT) has recently received much attention around the world as a treatment for AR and is now widely used to replace the subcutaneous route. SLIT has recently been introduced in Korea and is now available for AR treatment in the Asia-Pacific region. This review offers better understanding of SLIT for AR by summarizing published articles and our previous works regarding proposed mechanisms, indication and efficacy, safety and adverse events, and compliance.

Key words: Immunotherapy; Sublingual administration; Rhinitis

INTRODUCTION

The incidence of allergic rhinitis (AR) in the general population is currently around 10%-25%. Medical cost for AR treatment is increasing, and considering comorbid diseases including asthma, the treatment of AR has become more than just treating the rhinitis itself [1]. AR treatment can be classified into 4 categories: (1) avoidance and environmental control, (2) pharmacotherapy, (3) surgical treatment and (4) immunotherapy. Avoidance and environmental control is the safest way, but these are not always feasible. Intranasal corticosteroids and oral antihistamines have been accepted to be effective with few adverse effects. However, medical therapy only reduces allergic symptoms rather than reversing basic immunologic profiles of the AR patients. Surgical treatment is usually performed to correct structural problems which can aggravate nasal allergic symptoms and reduce the effective delivery of intranasal corticosteroids.

Allergen specific immunotherapy (SIT) has been studied and used for 1 century since Noon's first report in 1911 [2]. SIT is the only treatment option that modified fundamental allergic mechanism by inducing desensitization. At first, SIT was used for allergic diseases caused by pollen allergen, such as hay fever or

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seasonal AR, however today, indications extends to hymenoptera venom, house dust mites (HDMs), animal dander and allergic diseases for fungi [3]. Allergen extracts are injected intradermally. For safety, dosage starts at low concentration and increases slowly. When dosage reaches to maintenance concentration, maintenance dose is injected regularly for 3-5 years.

However, subcutaneous immunotherapy (SCIT) has several disadvantages. Patients have to visit clinicians' office regularly for injection and to tolerate the injection pain, and doctors should concern side effect such as anaphylaxis. Thus, SCIT is recommended to be performed only in facilities with adequate personnel and equipment that can effectively handle anaphylactic events [4]. Because of these inconveniences, other allergen administration methods including intranasal, oral, sublingual routes have been developed. Among them, sublingual immunotherapy (SLIT) has been widely used in European countries replacing SCIT because SLIT has several advantages: noninvasiveness, home administration, less frequency of severe adverse reaction than SCIT. The efficacy and safety of SLIT have been studied and in 2008, British Society for Allergy and Clinical Immunology announced SLIT as safe immunotherapy for AR and asthma [5] and in 2009, World Allergy Organization Position Paper about SLIT described its efficacy and safety [6]. This article discussed the proposed mechanism, indication, efficacy according to allergen, safety and compliance of SLIT.

Proposed mechanisms of SLIT

There are several studies that reported the immunologic changes of SLIT were similar to those of SCIT [7]. Both SLIT and SCIT are allergen specific immunotherapy, which derive 3 major immunologic changes: (1) regulation of allergen specific antibody response, (2) reduction of proinflammatory cell recruitment and activation, and (3) changes in allergen specific T cell response. In addition, we discuss about the oral (mucosal) tolerance as well as the 3 above-mentioned mechanisms.

(1) Regulation of allergen specific antibody response

It is typical characteristics of allergic disease that serum allergen specific IgE binds to FcεRI receptor on mast cell surface. Serum IgE level elevates in early phase of SCIT, but decreases several months after SCIT. This decline prevents seasonal rise of IgE in grass pollen allergic patients. However, early symptomatic improvement after immunotherapy does not relate to IgE level change because this change occurs in later phase of immunotherapy. Allergen specific IgG (mostly IgG1 and IgG4) rises, which relates to the clinical improvement. Also, IgA level sometimes increases [7].

In SLIT, similar to SCIT, the increase of allergen specific IgG4 level and the decrease of IgE/IgG4 ratio were observed. Recent meta-analysis reported that SLIT provoked significant change of allergen specific IgG and IgG4 level [8] and one another meta-analysis did that allergen specific IgG4 level increased and change in IgE/IgG4 ratio related to the reduction of skin reaction to allergen in later phase of SLIT and clinical improvement [9]. IgG4, known as blocking antibody, could antagonize and prohibit the allergic inflammation cascade resulting from antigen recognition by IgE. Therefore, the shift from IgE to IgG4 and change of IgE/IgG4 ratio is important for successes of immunotherapy [10]. Allergen specific IgE level changes were controversial [11-13]. The 2-year HDM SLIT treatment in asthmatic children did not show any differences in HDM-specific IgE between SLIT and placebo groups [11]. In our study on AR patients, specific IgE for *Dermatophagoides farinae* increased after 12-month SLIT, while specific IgE for *Dermatophagoides pteronyssinus* did not change significantly [12]. However, in grass pollen SLIT, time- and dose-dependent increases of Phleum pratense-specific serum IgE were found, indicating that the SLIT treatment had a significant allergen-specific effect on the immune system [13]. The change of IgA has also been reported. Antigen specific serum IgA rose in dose-dependent manner in SLIT with grass pollen allergen [13] and was up-regulated in SLIT with HDM allergen [14]. Thus, allergen specific IgG (and IgA) without any changes of IgE are thought to contribute to the clinical responses of SLIT.

(2) Reduction of proinflammatory cell recruitment and activation

SCIT reduces recruitment and activation of proinflammatory cells in mucosa related to allergic reaction. Recruitment and activation of mast cell, eosinophil and basophil decrease in the skin, the nasal cavity, the conjunctiva and the bronchial mucosa after allergen exposure when SCIT has been successful. SCIT induces peripheral T cell immune tolerance and regulates activation threshold of mast cell and basophil. Also, SCIT increases IL-10 production, which prohibits secretion of proinflammatory cytokines by mast cell, down-regulates functions and activities of eosinophil, and inhibits IL-5 production by Th0 and Th2 cells. Resembling these responses, SLIT decreased the level of basophil in the conjunctiva or the nasal cavity after allergen exposure. It was reported that the local or systemic eosinophil cationic protein (ECP) level was decreased in

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SLIT for grass pollen [15] and HDMs [12].

(3) Changes in allergen specific T cell response

The balance between Th1 and Th2 responses is crucial for allergic inflammation. SCIT induces Th1 response and reduces synthesis of Th2 cytokines. In grass pollen SCIT, the shift from Th2 profile to Th1 profile occurred in nasal mucosa or skin consistently although systemic change were not consistent. This results showed immunologic change is important not only in the peripheral blood but also in target organs.

It is the key step of SIT to maintain immunologic tolerance of peripheral T cell by antigen specific regulatory T cell. SCIT induces regulatory T cell, which secretes IL-10 and TGF-β [7, 16, 17]. IL-10 has several immunoregulatory functions on Th1 and Th2 responses. IL-10 promotes IgG4 rather than IgE class switching, and decreases MHC class II expression and activation and migration of mast cell and eosinophil [18]. TGF-β suppresses on both Th1 and Th2 responses, contributes to generate regulatory T cell subsets and induces B-cell immunoglobulin class switching to IgA [19].

T cell response in SLIT has not been fully elucidated. Some reported that SLIT with grass pollen did not have significant effect on T cell function including cytokine synthesis and cell proliferation and did not raise the counts of dendritic cell and T cell in epithelium and lamina propria [20, 21]. However, other studies using HDM SLIT, showed SLIT reduces IL-13, one of the Th2 cytokines, peripheral monocyte proliferation, ECP and prolactin [22, 23] and induces IL-10 production [24]. The reduction of prolactin level could reflect that T cell activity was reduced because prolactin is produced by activated T cell.

(4) Induction of oral mucosal immune tolerance

During SLIT, allergens are captured through FcεRI and/or other structures expressed by oral mucosal Langerhans-like DCs. DCs induce protolerogenic mechanisms in oral mucosa by the upregulation of coinhibitory molecule expression (B7H1 and B7H3) or release of IL-10 [25]. Allergen uptake of DCs attenuates their maturation and expression of chemokine receptor 7 (CCR7), being essential for the recruitment of DCs to peripheral lymphoid organs. Attenuated maturation and lower CCR7 expression of DCs after allergen uptake during migration to the lymphoid tissue might provide evidence of antigen presentation of DCs to T cells being performed outside local draining lymphoid tissues, ie, local contact of oral DCs with T cells in the oral mucosa [25]. Oral DCs are able to prime regulatory T (Treg) cells such as $CD4^+$ $CD25^+$ $Foxp3^+$ Treg cells, which increase in the oral epithelium during SLIT. Moreover, enhancement of $Foxp3^+$ Treg cells and IgG4 in peripheral blood as well as IL-10, IL-18 and signaling lymphocytic activation molecule in peripheral blood mononuclear cells was observed during SLIT [26, 27]. In addition, expression of programmed cell death ligand 1 on monocytes and B cells increased, while IL-4 production decreased in patients receiving pollen SLIT [28].

Indications of SLIT

In 2008, Allergic Rhinitis and its Impact on Asthma (ARIA) [29] suggested the indications for SLIT: (1) carefully selected patients with rhinitis, conjunctivitis and/or asthma caused by pollen and mite allergy, (2) patients insufficiently controlled by conventional pharmacotherapy, (3) patients who have presented with systemic reactions during injection-specific immunotherapy, and (4) patients showing poor compliance with or refusing injections.

SIT could apply to AR if the existence of allergen specific antibody and provocation of symptoms by the same allergen are proved [30]. To identify specific antigen, skin prick test (SPT) is preferred rather than multiple allergen simultaneous test which has lower sensitivity than SPT. Positive SPT result usually reflects the presence of antigen specific serum IgE, however, it should be correlated with clinical symptoms or AR history of the patients.

Some conditions relating patients' characteristics as well as AR itself should be considered. Poor compliance and bad communication would make it hard to evaluate symptom, efficacy and side effects of SLIT. One study reported that SLIT in very young children aged 1 to 3 years was safe [31], which suggests that age limitation does not seem to exist.

Efficacy of SLIT

Meta-analysis have proved SLIT had therapeutic efficacy for asthma and both adult and childhood AR [8, 9, 32-34], and the ARIA group acknowledged the efficacy of SLIT on rhinitis patients for birch, cypress, grass, olive, *Parietaria* and HDM in 2008 [29].

There are some initial studies that SLIT did not have desensitizing effect to HDM and grass pollen allergen comparing to placebo group [35, 36]. Moreover, SLIT had therapeutic efficacy on only severe AR and at least 3 year-treatment was required for clinical improvement [35]. As time goes, several studies for confirming SLIT efficacy have been conducted. One double-blind placebo-controlled (DBPC) studies including 855 patients with grass pollen AR showed moderate reduction of symptom score (16%) and medication use (28%) after 18-week treatment [37]. A recent meta-

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analysis showed that the patient with SLIT had less symptom (SMD, −0.49) and medication scores (SMD, −0.32) [8]. In our study of HDM SLIT in 88 patient with AR, all symptoms including nasal, eye discomfort and sleep disturbance were significantly improved 12 months after SLIT ($p < 0.05$) and a significant reduction of symptomatic medication use was observed between the first and 12 months ($p < 0.001$) [12].

The efficacy of SLIT in children has shown controversies. A study reported low dose allergen administration for 2 years to asthmatic children with HDM allergy did not change immunologic parameters [11]. In 2006, one meta-analysis for confirming efficacy of SLIT for pediatric AR patients 3 to 18 years of age showed a significant reduction in both symptoms (SMD, 0.56) and medication use (SMD, 0.76) after SLIT [38]. Recently, World Allergy Organization Position Paper reported that SLIT for pollen and HDM had the efficacy in children with AR ≥5 years of age and might be safely used in children ≥3 years of age [6].

The maintaining effects after discontinuation of SLIT has not yet been fully established although those of SCIT has been acknowledged [39]. A study including 137 patients with HDM AR showed that a greater improvement in the 3 years of SLIT compared with the 2 years of SLIT [40]. In another study with 15 years observation including mono-sensitized patients to HDM, clinical benefits of SLIT persisted for 7 years in patients with 3-year SLIT and for 8 years in those with 4, 5-year SLIT [41]. This study suggested that a 4-year SLIT is the optimal choice in present conditions because it induces a long-lasting clinical improvement similar to that of 5-year course and greater than that of a 3-year SLIT.

Preventive effect for asthma of SLIT has been established. In a study including 113 children with hay fever limited to grass pollen, development of asthma was 3.8 times less frequent in the SLIT group than in the control group after 3-year treatment [42]. Another study reported that 35 patients with allergic asthma/rhinitis due to HDM underwent SLIT for 4-5 years had significantly lower presence of asthma and use of antiasthmatic medication after SLIT, whereas 25 received only drug therapy had no change [43]. It also has been insisted that SLIT could prevent new allergen sensitization. One study reported that new sensitization appeared in 3.1% of 3-year SLIT patients although it appeared in 34.8% of patients who received drugs alone for 3 years [44].

Safety and adverse events

One of the advantages of SLIT over SCIT is the favorable safety profile. It is the safety that the most important advantage of SLIT comparing to SCIT. SCIT sometimes induces severe adverse side effects such as anaphylaxis. One DBPC study using grass and birch allergen reported 3.3% of patients received grass allergen and 0.7% of patients received birch allergen had systemic side effect [45]. Postmarketing surveillance study showed 0.9% of injection, 3.7% of patients underwent SCIT had systemic side effects [46].

According to a comprehensive review of published DBPC study, the adverse event rates were 23% in SLIT group and 12% in placebo group, and systemic events were 17% and 12%, respectively. Adverse event occurrences were not dose dependent and severe systemic reactions were not reported [47]. However, one DBPC study reported treatment related adverse events, irritation of the throat, and itching sensations in the mouth and ears, increased with dose [48]. There was no fatal event according to the report evaluating 66 studies including 4,378 patients, 1,181,654 administrations [49]. Forty one of 66 studies reporting adverse events showed 1,047 adverse events during 386,149 administrations (2.7/1,000 administration). Recent meta-analysis showed local reaction such as labial, buccolingual edema, buccal pruritus or throat irritation, and systemic reactions in the upper respiratory tract and associated organs (rhinitis, conjunctivitis or rhinoconjunctivitis) were more frequent in the SLIT group than in placebo group, however, asthma or wheeze occurred in similar rates in both SLIT and placebo groups and there was no fatality. Gastrointestinal problems were more common in SLIT group, especially children [8].

There were no mortality cases. Six cases with anaphylaxis, including 2 cases after using a mixture of multiple allergens, have been reported [50, 51]. One occurred in the treatment with latex rush protocol [52] and one developed after taking a dose 6-times (60 drops instead of 10 drops) greater than prescribed for HDM SLIT [53]. The remaining 2 occurred in the patients who had previously stopped SCIT due to severe systemic side effects [54]; a 13-year-old boy showed swelling of the tongue, angioedema of the eyes and generalized urticaria and a 27-year-old female experienced asthma symptoms, generalized itching and faintness with and abdominal cramps.

In our study, the incidence of adverse effects of SLIT was 52.1% (48 of 92 patients) during first 30 days, up-dosing phase [55]. Aggravation of AR symptoms was the most common adverse events during this phase. After 6 months or more, 13 patients (14.1%) experienced temporary adverse events such aggravation of symptoms, itching sensation in the oral cavity/lips/eyes/skin,

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gastrointestinal symptoms and breathing discomfort. However, these adverse events subsided spontaneously without medication. None of the patients needed to visit an emergency room.

Safety of SLIT in younger children has been studied. One study involving 65 children aged 3-7 years showed that side effects including urticaria, oral pruritus and gastrointestinal problem in children younger than 5 years were not severer than those in children aged 5-7 years [56]. Another study on 126 pediatric patients, aged 3-5 years, confirmed that SLIT is also safe in children under the age of 5 years [57]. Nine side effects in 7 children (5.6% patients and 0.2/1,000 doses) were reported and all side effects occurred during up-dosing phase: 6 gastrointestinal side effects, 2 oral itching and 1 mild abdominal pain. All problems were solved by reducing dosage. The other study showed multiple allergen SLIT in children did not have more risk of adverse reaction than mono-allergen SLIT [58].

Compliance of SLIT

Compliance is critical problem for continuing SLIT because patients administer allergen by themselves or their parents. The drop-out rates which conducted in European countries were 5%-30% in treated subjects [59-62]. In Korea, the drop-out rate of our series for 6 months were 31%, which was relatively high [55]. The most common reason of drop-out was inability to take medication according to schedule. Thus, convenient allergen formula and application schedule needs to be developed, and proper and prudent management of the patients is needed to reduce the drop-out rate.

CONCLUSION

SLIT has been establishing its role for AR. SLIT could be adopted for both adult and children patients with AR for pollen or HDM with safety. Long-term use of SLIT could change immunologic profiles. SLIT as well as SCIT does not make only clinical symptom improve but also prevents poly-sensitization and development of asthma. Also, risk of severe or fatal adverse events seemed to be much less than SCIT.

However, there are still many unsolved problem. The duration and optimal dosage of SLIT are not well established. The effect duration after discontinuance of SLIT should be investigated more. The effect of SLIT in poly-sensitized patients and appropriate dose interval are still uncertain. Also, many of studies about SLIT have been conducted in European countries for Caucasian patients. Thus, further SLIT studies in Asia-Pacific region are needed.

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