World Journal of Immunology

Submit a Manuscript: http://www.wjgnet.com/esps/
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
DOI: 10.5411/wji.v4.i3.130

World J Immunol 2014 November 27; 4(3): 130-140
ISSN 2219-2824 (online)

REVIEW

Subcutaneous and sublingual immunotherapy: Where do we stand?

Ayfer Yukselen, Seval Guneser Kendirli

Ayfer Yukselen, Clinic of Pediatric Allergy and Immunology, Gaziantep Children Hospital, 27560 Gaziantep, Turkey
Seval Guneser Kendirli, Clinic of Pediatric Allergy and Immunology, Cukurova University Faculty of Medicine, 01330 Balcali, Adana, Turkey
Author contributions: The collection of documents, the review of articles published up to day about immunotherapy and writing of the manuscript were made by Yukselen A; Kendirli SG consulted and contributed to the manuscript with her valuable comments.
Correspondence to: Ayfer Yukselen, MD, Clinic of Pediatric Allergy and Immunology, Gaziantep Children Hospital, Osmangazi mah., Sehitkamil, 27560 Gaziantep, Turkey. ayfyukselen@gmail.com
Telephone: +90-342-2200072 Fax: +90-342-2200072
Received: March 29, 2014 Revised: May 1, 2014
Accepted: July 12, 2014
Published online: November 27, 2014

Abstract

Though symptoms of allergic diseases can be reduced by the use of drugs such as corticosteroids, antihistamines or leukotrien antagonists, the only treatment directed to change the natural course of allergic disease is allergen-specific immunotherapy (SIT). Its efficacy can last years after the cessassion of the treatment. SIT brings on regulatory T cells with the capacity to generate interleukin-10 and transforming growth factor-b, restricts activation of mast cells and basophils, and shifts antibody isotype from IgE to the noninflammatory type immunoglobulin G4. Subcutaneous (SCIT) and sublingual (SLIT) immunotherapy are the two most used ways at the present for applying SIT. These two treatments were demonstrated to be effective on reducing symptoms and medication use, in prevention of new sensitizations and in protecting from progression of rhinitis to asthma. The safety of SLIT appears to be better than SCIT although there have been a few head to head comparisons. In order to overcome compliance problems or possible systemic side effects which may be faced during this long-term treatment, recent investigations have been focused on the implementation of allergens in quite efficacious and safer ways.

Key words: Asthma; Efficacy; Rhinitis; Safety; Subcutaneous immunotherapy; Sublingual immunotherapy

Core tip: Specific allergen immunotherapy is the unique treatment method capable of changing the natural course of allergic disease. Both Subcutaneous (SCIT) and sublingual (SLIT) may act as efficient treatment options in patients with allergic rhinoconjunctivitis and asthma. In this paper, we reviewed clinical efficacy and safety of both SCIT and SLIT in allergic respiratory diseases by discussing recent studies.

Yukselen A, Kendirli SG. Subcutaneous and sublingual immunotherapy: Where do we stand? *World J Immunol* 2014; 4(3): 130-140 Available from: URL: http://www.wjgnet.com/2219-2824/full/v4/i3/130.htm DOI: http://dx.doi.org/10.5411/wji.v4.i3.130

INTRODUCTION

The number of allergic respiratory diseases such as allergic rhinitis (AR) and asthma has gone up in the past twenty years in both children and adults around the world[1]. The estimation reveals that up to 20% of the United States and Western Europe populations are likely to be affected by allergic respiratory diseases[2]. These diseases may impact the quality of life, work and educational performance, which can lead to an important individual and economic lost. Pharmacotherapy provides symptomatic relief and is effective in most cases, however, no sustainable benefit is provided when the treatment is ended. Moreover, some patients fail tolerating pharmacotherapy in both rhinitis and asthma, and some various publica-

tions have reported only limited control of symptoms[3,4].

Allergen-specific immunotherapy (SIT) was first implemented by Noon[5] in 1911, and represents till now the sole treatment targeted to address the cause of IgE-mediated allergic diseases[6]. It is also the unique treatment which is able to shift the natural course of the respiratory allergic diseases by ameliorating symptoms[7], lessening the need to medications[7] and preventing progression from rhinitis to asthma[8,9]. In addition, it offers permanent benefit years after the treatment is stopped. The basic principle of SIT is to induce immune tolerance to allergens by administering them to patients in repeated, increasing doses[10].

The effectiveness of the most used routes, subcutaneous (SCIT) and sublingual (SLIT) immunotherapy, is referenced for perennial along with seasonal allergic respiratory diseases by systematic reviews and meta-analyses[7,11-13].

There is not any specific criteria that can help to identify which one of these routes should be selected. The first used method of administration was subcutaneous. But, lots of research data encourage the use of SLIT because of the discomfort of repeated injections and higher risk of adverse reactions. Recently, allergy immunotherapy tablets have also been used for patients with respiratory allergies and sold in some countries for both adults and children. The most common indoor and outdoor allergens covered by allergy immunotherapy tablets may replace sublingual drops in the near future.

This review will be focus primarily on the clinical efficacy and safety of both SCIT and SLIT in allergic respiratory diseases, particularly in asthma and AR, in the light of recent literature.

Induction of tolerance and immunologic changes during SIT

The main mechanism of action of SIT involves alterations in the configuration of allergen-specific memory T and B cell reactions, the synthesis of particular antibody isotypes that incline the immunologic response towards non inflammatory patterns, along with reducing activation, tissue migration and degranulation of effector cells including mast cells, basophiles and eosinophiles[14]. Early suppression of innate effector cells of allergic inflammation, regulation of Th2 type responses have been demonstrated to occur both in the tissue and in the peripheral blood during SIT[6,14,15].

Another significant mechanism linked to the use of SCIT and SLIT is the appearance and activity of FOXP3+ CD25+ Treg cells. These cells can produce IL-10 and transforming growth factor-b (TGF-b) to inhibit activity of allergen-specific Th2 cells with the following recruitment of other inflammatory effector cells. In addition, the production of IL-10 and TGF-b from Treg cells stimulates B cells to undergo class switching and produce the noninflammatory antibodies IgG4 and IgA2[16-18]. IL-10-secreting Breg cells can inhibit effector T cells and selectively induced IgG4 antibodies to contribute to allergen tolerance[14,16].

Unlike SCIT, SLIT is demonstrated to work slightly different. Actual models of SLIT proposes an uptake of allergen by antigen-presenting cells in the oral mucosa, pursued by migration to regional lymph nodes[19]. Subsets of dendritic cells found in epithelium and subepithelium of oral mucosa were presented to be effective at allergen uptake *in vitro* and capable of inducing T cells secreting IFN-g and/or IL-10 with production of IgG1 and IgG4 antibodies[20].

During SIT, an increment have also been observed in IL-12 which is a potent Th1 cell cytokine[21]. Consequently, these events lead to shifting from a Th2 cell pattern of response to more of a Th1 and Treg cell pattern which also reflects allergic tolerance and thus clinical improvement in allergic diseases[22]. Both early and late-phase allergic reactions can be inhibited in peripheral tissue such as skin, nose or lungs by SIT[23,24].

An important increment in serum-specific IgG4 and serum allergen-specific IgA, in addition increases in IL-10 and TGF-b are some alterations demonstrated after allergen specific immunotherapy[25]. Moreover, the important role of T-regulatory cells in the induction of allergen-specific tolerance was also confirmed by the local presentation of FOXP3+CD25+ T-cells in the nasal and sublingual mucosa after immunotherapy[22].

Clinical effectiveness of SCIT in rhinitis

Frew *et al*[26] demonstrated that one season of immunotherapy with grass pollen decreased symptoms and medication use and ameliorated the quality of life of patients with moderately severe allergic rhinitis.

A Cochrane review of SCIT in seasonal AR due to tree, weed or grass pollens involved 51 studies based on 2871 individuals both adults and children[11]. Symptom scores from 15 studies showed an important reduction in the SCIT group [SMD-0.73 (95%CI: -0.97 to -0.50, $P < 0.00001$)], and medication use from 13 studies demonstrated a significant decrease in the group of SIT [SMD of -0.57 (95%CI: -0.82 to -0.33, $P < 0.00001$)]. Furthermore, most of these studies included in this review, reported that nasal and bronchial symptoms along with quality of life scores, and all of the clinical parameters improved in favor of the immunotherapy groups.

In 2007, the update of Global European Allergy and Asthma Network stated that SCIT studies carried on the last 10 years confirmed these results and declared that SCIT was particularly efficacious in improving of symptoms and decreasing of medication consumption in grass, birch, *Parietaria*, mite and ragweed allergy[27].

The significant improvement in symptoms and quality of life as well as reduction in seasonal bronchial hyperresponsiveness were also reported in various studies of grass-pollen SCIT[28,29].

In a meta-analyses included 44 studies of house dust mite (HDM) immunotherapy for AR and asthma, it was stated that, though SCIT was found effective, the magnitude of effect varied greatly from one study to another[30].

Three studies performed in patients with HDM-induced AR demonstrated a significant difference between active and placebo, in terms of symptom scores[31,32] and nasal VAS after one-year treatment[33].

It was also reported that SCIT with animal dander, especially in patients with rhinoconjunctivitis due to cat allergy is capable to reduce symptom scores and decrease skin test responses[34].

Clinical effectiveness of SLIT in rhinitis

The first meta-analysis on SLIT for the treatment of allergic rhinitis involved 979 patients in 22 trials which all of them were double-blind, placebo- controlled and published up to 2002[35]. Six of these SLIT studies were performed in patients sensitized with house dust mite, five with grass pollen and *Parietaria*, two with olive and one with respectively ragweed, cat, tree and cupressus. This meta-analysis revealed that SLIT was significantly effective in comparison to placebo regarding the decrease in both symptoms and medication use.

A meta-analysis which was in the framework of Cochrane review included 49 studies which 23 of them for grass, nine trees, five for *Parietaria*, two for ragweed, eight for dust mites, one for cat, and one for mixed pollens[12]. There was 2333 patients receiving SLIT and overall, there was significant decrease in symptoms (SMD, -0.49; 95%CI: -0.64 to -0.34) and medication requirements (SMD, -0.32; 95%CI: -0.43 to -0.21). As individual allergens were evaluated, there was significant improvement in symptoms for house-dust mites, grass pollen, ragweed, *Parietaria*, and trees.

Another meta-analysis, included four studies for mites, three for grass, one respectively for *Parietaria* and olive, and one for pollen mix and totally 484 patients (most of them are children)[36]. A considerable reduction in both symptoms and rescue medication use was detected. This meta-analysis showed that, treatment duration of > 18 mo and SLIT with pollen extracts were more beneficial than shorter treatment durations and dust-mite antigens.

In GA2LEN meta-analysis of SLIT for house-dust mite allergic rhinitis demonstrated significant symptom and medication reduction in 194 active SLIT-treated patients in comparison to 188 placebo participants[13].

Recently, allergy immunotherapy tablets have been marketed for using in patients with allergic respiratory diseases. The studies conducting to investigate the efficacy of grass pollen tablets in allergic rhinitis revealed significant decrease in symptom and medication scores during pollen season[37-40]. In a study involved 509 adult patients with HDM-allergic rhinitis published recently, it was reported that twelve months of treatment with sublingual tablets of HDM allergen extracts was effective and well tolerated[41].

Clinical effectiveness of SCIT in asthma

There are lots of studies which assessed the effectiveness of SCIT in asthma in the literature. The first results of these studies was published in 1995 by Abramson[42] and then updated several times in the framework of Cochrane review[7,43,44].

In a recent Cochrane review, 88 trials of SCIT were evaluated[7]. The studies included in this review involved 3459 patients suffering from asthma and reported the results of SCIT for dust mites (42 studies), pollen (27 studies), animal dander (10 studies), molds (2 studies), latex (2 studies), and multiple allergens (6 studies). It was concluded that SCIT improved asthma symptoms, reduced drug requirement and diminished bronchial hyperresponsiveness. Additionally, it was noted that the reduction in symptoms was more pronounced by both mite and pollen immunotherapy.

There are also other SCIT studies with dust mites in adult and pediatric patients also showed amelioration in symptoms, decreasing in medication requirements and BHR[31,45-47].

Several studies of SCIT, particularly with mites[48,49] or mixed-allergen up to seven aeroallergens[50] showed minimal improvement in medication scores, symptom scores and PEF. Although significant steroid- sparing effect of immunotherapy was observed in moderate persistent asthmatics included in those studies, it is important to maintain asthma control during the study in order to obtain maximum benefit from the immunotherapy.

Clinical effectiveness of SLIT in asthma

The effectiveness of SLIT in asthma has been evaluated in many studies and meta-analyses. However, in most of these studies asthma assessment was performed in combination of rhinitis and rarely was the primary outcome. Therefore, we need to carefully designed studies of SLIT carried particularly on asthmatic patients[51].

In 2009, the World Allergy Organization Position Paper on Sublingual Immunotherapy discussed a number of important points regarding the current status of SLIT efficacy[52]. It has been stated that although SLIT meta-analyses have shown effective to address allergic rhinitis in adults, allergic rhinitis and asthma in children, there are limitations about the conclusions of these meta-analyses because of the significant heterogenity between the studies included in them.

A meta-analysis in asthma involving 25 studies based on 1706 participants of about whom eight trials were for mites, 14 trials for pollen, one trial for latex, and two for mixed allergens showed an important effect of SLIT for symptoms and medication requirements when all allergic symptoms and medication use for both allergic rhinoconjunctivitis and asthma were evaluated together[53]. But, when we analyse the asthmatic symptoms and decrease in use of specific asthma medication as constant outcomes, it appears that this decreases is not remarkable (SMD, -0.38 and -0.91). The authors then suggested that even though the evidence is not very strong, SLIT ameliorated some parameters of asthma, may be in a lesser proportion than SCIT.

Another meta-analysis of SLIT in asthma involved nine studies on 441 participants whom ages vary from 3

to 18 years. Within this trials, six included dust mites- and three included pollen- allergic patients. When compared with placebo, a considerable reduction in symptom (SMD, -1.14; 95%CI: -2.10 to -0.18) and medication scores (SMD, -1.63; 95%CI: - 2.83 to -0.44) was noted with SLIT[54].

A different meta-analysis evaluated nine trials about 452 both adults and children with asthma treated with house dust mite SLIT. This meta-analysis demonstrated notable improvement in symptom and medication scores[13].

Another meta-analysis of seven trials conducted on 256 children showed significant decreases both in symptoms and medication use related to asthma; the authors deduced that sublingual immunotherapy is a safe and effective treatment option in respiratory allergies[55].

Additionally, an important finding observed in some pollen studies is the delay in positive results to the second year of treatment[56,57].

Recently, in a study involving 602 asthmatic patients who are sensitized to house dust mites, it was reported that daily treatment with SLIT tablet reduced inhaled budesonide more than 80 ug/d in comparison to placebo after 1 year[58]. Similarly, the steroid sparing effect of SLIT was also shown in birch pollen allergic patients with asthma[59].

Long-term effects of SCIT and SLIT

SIT provides both clinical and immunologic tolerance as specified by the persistence of clinical improvement and associated long-term immunological parameters after stopping the treatment. Additionally, long-term benefits of SIT include prevention of new sensitizations in monosensitised patients and progression from rhinitis to asthma particularly in children.

A study with grass pollen immunotherapy showed that there is no remarkable difference in symptoms and medication use in the following three years after 3-4 years of SCIT[60].

A recent HDM study[61] evaluated the long-term effect of either 3 or 5 years time duration of subcutaneous immunotherapy in 240 patients. The first year of this study was a double-blind placebo-controlled phase; after treatment of 3 years with HDM SCIT, one group was then followed for 2 years without any treatment, while the other group kept being under treatment for 5 years. When the patients were assessed after a period of 3 and 5 years of treatment, both groups had considerable amelioration of symptoms compared to baseline, revealing more than 70% reduction in rhinitis symptoms in the 5-years group while 50% reduction in the 3-years treatment group.

There are also some studies supporting the persistence of improvement in symptoms along with preventive effects on new sensitizations and asthma development that continued for years after ending of treatment in children with allergic rhinitis given 3-years immunotherapy[62,63].

It has been documented that SCIT with a single allergen has a preventive effect against sensitization to different inhalant allergens[64-67].

Recent studies have shown such effects with SLIT. One of them is an open, randomized study involved 216 children with allergic rhinitis by Marogna *et al*[68]. This study showed significant reduction in development of new sensitizations in children receiving SLIT (3.1%) when compared with controls.

A SLIT study included 257 patients with grass pollen allergy by Durham *et al*[69] demonstrated persistence in reduction of rhinoconjunctivitis scores related to symptoms and medication use in the SLIT group at the 1-year period after ending of 3-year SLIT[69]. Finally, Marogna *et al* have noted that clinical benefit persists for 8 years after SLIT treatment is given for a 4- to 5-year duration; new sensitizations were also reduced in SLIT groups[70].

SAFETY

Safety of SCIT

Patients treated with SCIT have run a risk of both local and systemic adverse reactions but, in most cases, symptoms are reversible if they are diagnosed early and treated immediately. All allergen preparations such as standardized extracts[27], allergoids[71] or recombinant allergens[72] may lead to side effects during treatment.

The incidence of systemic reactions of SCIT varies between 0.06% and 1.01% in those receiving injections[73]. The vast majority of reactions occured during SCIT were reported as mild and death is infrequent (*i.e.*, incidence is about one per million to one per 2 million injections)[73].

A recent Cochrane review revealed that epinephrine was administered in 0.13% of injections in the SCIT group while this rate was 0.01% in the placebo group. No fatalities was reported in this review. Local reactions were seen frequently in the SCIT group in comparison to placebo (92% *vs* 33%)[11].

Almost all cases of fatality due to SCIT reported previously were patients having asthma that was frequently poorly controlled[74]. Therefore it should be kept in mind that uncontrolled asthma is a contraindication to initiation of SCIT as stated in guidelines.

Safety of SLIT

The safety of SLIT seems to be better than that of subcutaneous immunotherapy regarding the occurrence of severe systemic reactions. The serious adverse effects such as anaphylaxis described during sublingual treatment are rare[75-79]. A recent meta-analysis for SLIT in AR showed that there are no cases of severe systemic reaction or anaphylaxis, and there was no need to use epinephrine for any of the systemic reactions[12].

Indications to SLIT were extended in some official documents to "Patients with systemic reactions after subcutaneous immunotherapy"[80]. However, there are also some reports on patients who had ceased this treatment since adverse reactions and severe anaphylactic reactions to SLIT[79]. Therefore, it has been recommended that immunotherapy should be customized for each patient

based on the intensity of sensitization, accompanying allergies, environmental exposures, and other risk factors.

Local side effects such as perioral itching or mild swelling are seen particularly in the early phase of SLIT and encountered in about three-fourths of patients. Nausea, abdominal pain mainly in children, rhinitis, conjunctivitis, headache, urticaria, cough and bronchospasm are other infrequent side effects which may ocur during SLIT[81].

Head-to-head studies

There are a few studies which compare SCIT and SLIT directly[31,81-88]. A summary of the characteristics of SCIT *vs* SLIT comparison studies is shown in Table 1.

The study of Mungan *et al*[83], consisted of 36 adults with HDM-allergic rhinitis and asthma; they randomized to treat with SCIT, SLIT or placebo. It was found that one-year SCIT improved symptom scores of both rhinitis and asthma when SLIT was effective only for symptoms of rhinitis. However, they reported that though no notable alteration was recorded in placebo group in terms of symptom and medication scores, drug requirement was significantly reduced in both SCIT and SLIT groups.

A placebo-controlled double-blind double-dummy study (all patients received both sublingual medication and subcutaneous injections) carried on 71 adults with allergic rhinitis sensitized to birch pollen was reported by Quirino *et al*[82] in 2004. This particular study showed that both routes of treatment were effective in the reduction of symptoms and medication use when compared with placebo arm. They concluded that SLIT decreased the median disease severity to one-half and SCIT to one-third of placebo treatment. There was not found statistically significant difference between SCIT and SLIT.

Another study compared SCIT with SLIT in patients sensitized to grass pollen was also designed in double-blind double-dummy manner[84]. This study demonstrated that both SCIT and SLIT meet the same effectiveness according to subjective clinical outcomes. Both treatment mode reduced significantly symptoms and drug usage ($P = 0.002$ for symptoms and drugs in SLIT-treated patients; $P = 0.002$ for symptoms and $P = 0.0039$ for drugs in patients given SCIT). But, in this study, alteration in immunologic outcomes (total specific IgG, specific IgG4, skin reactivity) was observed only in SCIT group.

A study published in 2007 by Mauro *et al*[86] included patients with allergic rhinitis sensitized to *Betulaceae* and showed that there was no significant difference between patients received SCIT and SLIT in terms of symptom scores and medication consumption. It was also noted that although the increment in Bet v 1 specific IgG4 was observed in both treatment arms, it reached statistically significant levels only in patients received SCIT.

Eifan *et al*[85] published the results of a study which conducted in an open design and included 48 children with asthma/rhinitis sensitized to HDM. The patients were randomized to receive either SCIT, SLIT or pharmacotherapy. Both SLIT and SCIT demonstrated significant improvement in symptom and medication scores as well as in visual analog scores for both rhinitis and asthma, in severity of skin and nasal sensitization to specific allergen in comparison to the pharmacotherapy group. In this study, both SCIT and SLIT had decreased disease severity more than half than the severity observed in pharmacotharapy group. The authors concluded that SCIT and SLIT are equally effective in the control of the disease severity.

Another study which evaluate the efficacy of three-years SCIT and SLIT in total 193 HDM allergic patients with perennial rhinitis showed that although both treatment mode effective, greater improvement was observed in SCIT group in comparison to the SLIT group[88].

In a recent open-scheme, prospective study involving 60 children (5-12 years of age) with asthma/rhinitis sensitized to HDM, patients were randomized to receive either SCIT, SCIT plus SLIT, SLIT or pharmacotherapy[87]. Children were evaluated for symptom/medication scores, allergen- specific nasal reactivity and Der p 1-driven cytokine responses at baseline, 1, 4 and 12 mo. The improvement in symptom and medication scores was observed earlier in the SCIT group than the SLIT group (4 mo *vs* 12 mo). This study concluded that subcutaneous route of immunotherapy appeared more effective in comparison to the sublingual route since it provided earlier clinical efficacy along with earlier induction of regulatory cytokines and production of IgG_4 antibodies. Nevertheless, combining these two routes of immunotherapy looks promising particularly in children because of obtaining significant clinical efficacy with the advantage of fewer injections.

A randomized, placebo-controlled, double- dummy trial investigating the efficacy of SCIT and SLIT in children with asthma and/or rhinitis sensitized to HDM was published in 2012[31]. This particular study indicated that one-year SCIT reduced significantly symptoms and medication consumption related to both rhinitis and asthma. SLIT decreased symptoms of rhinitis and asthma in addition to medication scores for rhinitis, but this lessening was not found significant in comparison to the placebo group. Only SCIT was recognized to have a superior effect to placebo on reduction of rhinitis and asthma symptoms after one-year of treatment. The same cohort was then followed for the one subsequent year in an open scheme and the placebo group was randomized to have SCIT or SLIT, and for 1 year all patients received active treatment with SCIT or SLIT[89]. This latter study demonstrated that the effect of SLIT on symptoms and drug usage related to asthma was less prominent than SCIT in the first year, but it increased in the second year of SLIT. The conclusion of this study is, although both clinical and immunologic improvement with SCIT begins from the first year of immunotherapy, it requires longer treatment with SLIT in HDM-sensitized children with rhinitis and asthma.

The fact of immunotherapy has also some placebo effect has been accepted since long time. Although there

Table 1 Head-to-head study characteristics with subcutaneous and sublingual

Ref.	Year	Allergen	Study design	No. of patients	Findings
Quirino *et al*[84]	1996	Grass pollen	Double-blind, double-dummy	SCIT (n = 10) SLIT (n = 10) No placebo group	Significant reduction in symptoms and medications for SCIT and SLIT groups ↑ Total specific IgG, ↑specific IgG4 and ↓skin reactivity for SCIT only
Mungan *et al*[83]	1999	Dust mite	Single-blind, placebo controlled	SCIT (n = 10) SLIT (n = 15) Placebo (n = 11)	↓ Rhinitis symptoms with SLIT ↓ Skin reactivity with SCIT ↑ Specific IgG4 with SCIT
Khinchi *et al*[82]	2004	Birch pollen	Randomized, double-blind, double-dummy, placebo-controlled	SCIT (n = 21) SLIT (n = 18) Placebo (n = 19)	Significant reduction in symptoms and medications for SCIT *vs* placebo and SLIT *vs* placebo No difference between SCIT and SLIT groups
Mauro *et al*[86]	2007	Birch pollen	Randomized, double-blind, double-dummy	SCIT (n = 19) SLIT (n = 15)	No difference in mean symptom and medication score between SCIT and SLIT Specific IgG4 with SCIT
Tahamiler *et al*[88]	2008	Dust mite	Open label, randomized	SCIT (n = 96) SLIT (n = 97)	↓ Rhinitis and conjunctivitis symptoms scores and nasal provocation score with SCIT and SLIT (greater improvement with SCIT)
Eifan *et al*[85]	2010	Dust mite	Open label, randomized, controlled	SCIT (n = 16) SLIT (n = 16) Pharmacotherapy (n = 16)	↓ Rhinitis and asthma symptom score, total medication score ↓ Skin reactivitiy with SCIT and SLIT ↓ Specific IgE with SCIT and SLIT
Keles *et al*[87]	2011	Dust mite	Open label, randomized, controlled	SCIT (n = 11) SLIT (n = 13) SCIT plus SLIT (n = 14) Pharmacotherapy (n = 12)	Reduction in total symptom score and total medication score in all immunotherapy groups ↓ Skin reactivity with SCIT ↑ Specific IgG4 for SCIT and SCIT plus SLIT
Yukselen *et al*[89]	2012	Dust mite	Randomized, double-blind, double-dummy, placebo-controlled	SCIT (n = 10) SLIT (n = 11) Placebo (n = 10)	Significant reduction in rhinitis and astma symptom score with SCIT Skin reactivity with SCIT and SLIT ↑ Specific IgG4 with SCIT

SCIT: Subcutaneous immunotherapy; SLIT: Sublingual immunotherapy.

is heterogeneity between many immunotherapy trials, most of them showed significant improvement in clinical outcomes and immunologic parameters in comparison to the placebo. Both SCIT and SLIT have proven to be effective in both rhinitis and asthma. However, the two trials[31,82] (one in birch pollen -allergic adults and another in mite- allergic children) designed with double-dummy arms as recommended to obtain more valuable results showed greater efficacy of SCIT than SLIT for clinical improvement of rhinitis.

A systematic review of trials involving direct comparison of SCIT and SLIT regarding the efficacy and safety in the treatment of allergic rhinitis and asthma was published recently[90]. It included 8 randomized controlled trials with 555 subjects published between 1989 and 2011, comparing the effectiveness of SCIT with SLIT[81,82,84-88,90]. Three studies included only adults[82,83,86] and 2 included both adults and children[87,90]. The mean age of the subjects ranged between 6 and 40 years. Three studies had only SCIT and SLIT arms[86,88,91]. In addition to SCIT and SLIT arms, 3 studies had a placebo arm[31,81,82] and 2 studies had a pharmacotherapy arm[85,87]. Two trials included patients with allergic rhinoconjunctivitis and rhinitis to tree pollen[82,86]. The remaining 6 trials studied dust mite immunotherapy, 2 of which were exclusively in patients with rhinitis[88,91] and 4 in patients with rhinitis and/or asthma[31,82,84,86]. As the result of systematic analysing of all these head-to-head studies, it was noticed that low-grade evidence confirms more pronounced efficacy of SCIT for asthma symptom reduction and also for decreasing of symptoms and medication use related to rhinitis in comparison to SLIT; there was also moderate-grade evidence which supports better efficacy of SCIT than SLIT for reduction of nasal and/or eye symptoms. More studies are needed to fortify this evidence so as to make clinical decision.

CONCLUSION

SIT is an immunologically based treatment which can modify the natural course of IgE-mediated allergic respiratory diseases. Despite the significant heterogeneity in study design, there is considerable evidence to defend the whole efficacy and safety of both SCIT and SLIT for treating allergic rhinoconjunctivitis and asthma.

Although the two routes proved equivalent in terms of efficacy in some head-to head comparisons, the question of "which one of these routes should be preferred in allergic diseases?"may be discussed. When this recommendation has been made, it should be considered not only the clinical effectiveness together with the quality of evidence, but also safety, costs, and patient's preference and adherence. There are also some limited rate patients shifted from SCIT to SLIT or vice versa. The most common reasons reported in allergic children who shifted from SLIT to SCIT are a perceived low efficacy of the

treatment and local side effects. On the other hand, frequent discomfort and side effects caused by injections are main causes of interrupting of SCIT. The patient's adherence to treatment mode is also an important factor in choosing the the route of immunotherapy. The improved adherence is expected in SLIT, because it does not require much treatment-related patient time. Similarly, SLIT's favorable safety profile which allows home administration is expected to improve the convenience of immunotherapy and to rise the rate of patients taking this treatment mode. However, several studies have indicated that SLIT adherence is equally as poor as SCIT. Therefore, the treatment mode of immunotherapy should be individualized for each patient according to patient's perception, adherence and preference. Additionally, in multiple allergen sensitization, it may be more convenient to prefer the SCIT to SLIT.

Because of long-term duration of treatment and possible side effects with SIT, novel safer and faster methods or administration routes have been investigated. Different approaches have been performed to improve the safety and efficacy by adding adjuvants, like Monophosphoryl lipid A (MPL), DNA sequences or bacteriophage combined with cytosine phosphodiester guanine (CpG) oligodeoxynucleotides (ODN), or by modifying the allergen itself, or using recombinant allergens. In these cases, T-cell epitopes should ideally be preserved so that the resulting hypoallergen will still be able to modify the allergen-specific immune response[92].

In addition to allergen modification, recombinant allergens and adding adjuvants, the trials have concentrated on the ways of administration. A newly described procedure is engineering modular antigen translocating (MAT) molecules for intracellular targeting of allergens to the major histocompatibilityclass-Ⅱ (MHC-Ⅱ) presentation pathway to reinforce antigen presentation. MAT-allergen fusions are capable of quickly translocating into the cytoplasm of PBMCs, gather intracellulary and bring on potent proliferation of PBMC cultures showing an increased presentation through the MHC-Ⅱ presentation pathway. In PBMC cultures of allergic donors, MAT vaccines lead to change in cytokine profile from Th2 to Th1, and reduce the secretion of IL-4, IL-5 and IL-2 in comparison to those induced by the corresponding recombinant allergens[93]. As a result, MAT molecules represent promising compounds for the development of strong allergy vaccines.

There is a growing interest in intralymphatic allergen specific immunotherapy (ILIT) because it is a highly efficacious and safe treatment route that requires only 3 injections. Recently, the results of ILIT performed by guidance of ultrasonograpy in humans was reported[94]. This trial was designed as a double-blind, placebo controlled manner using the recombinant major cat dander allergen Fel d 1-MAT molecule. After only three injections, it was shown significant increment in nasal reactivity to the allergen in the ILIT in comparison to the placebo group. It was also noted that there was pronounced responses in T regulatory cells and IL-10 in the ILIT group.

One more ILIT study reported also recently was a double-blind, placebo-controlled trial, and included patients having allergic rhinitis sensitized to birch or grass pollen[95]. This study showed that three intralymphatic inguinal injections of pollen induced significant reduction in nasal symptoms after nasal provocation.

Epicutaneous immunotherapy (EPIT) is one more new way of administering in SIT. In a recent placebo controlled, double-blind study involved 132 patients with grass pollen-induced rhinoconjunctivitis, it was demonstrated that EPIT which performed as 6 weekly patches, decreased symptoms significantly both during the pollen period and subsequent year[96]. Epicutaneous allergen-specific immunotherapy is a promising way of administration since its ability to provide a safe, needle-free, and self-administrable treatment option. Further well-designed controlled studies will help discover the optimal regimen for SIT efficacy and safety.

REFERENCES

1 **Eder W**, Ege MJ, von Mutius E. The asthma epidemic. *N Engl J Med* 2006; **355**: 2226-2235 [PMID: 17124020 DOI: 10.1056/NEJMra054308]

2 **Bauchau V**, Durham SR. Prevalence and rate of diagnosis of allergic rhinitis in Europe. *Eur Respir J* 2004; **24**: 758-764 [PMID: 15516669 DOI: 10.1183/09031936.04.00013904]

3 **Soyer OU**, Beyhun NE, Demir E, Yildirim S, Boz AB, Altinel N, Cevit O, Karakaş T, Anlar Y, Söğüt A, Altintaş D, Canitez Y, Büyükdereli Z, Sekerel BE. A multicenter survey of childhood asthma in Turkey. II: Utilization of asthma drugs, control levels and their determinants. *Pediatr Allergy Immunol* 2009; **20**: 172-179 [PMID: 18823358 DOI: 10.1111/j.1399-3038.2008.00769]

4 **Demoly P**, Gueron B, Annunziata K, Adamek L, Walters RD. Update on asthma control in five European countries: results of a 2008 survey. *Eur Respir Rev* 2010; **19**: 150-157 [PMID: 20956184 DOI: 10.1183/09059180.00002110]

5 **Noon L**. Prophylactic inoculation against hay fever. *Lancet* 1911; **177**: 1572-1573

6 **Akdis CA**, Akdis M. Mechanisms of allergen-specific immunotherapy. *J Allergy Clin Immunol* 2011; **127**: 18-27; quiz 28-29 [PMID: 21211639 DOI: 10.1016/j.jaci.2010.11.030]

7 **Abramson MJ**, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2010: **(8)**: CD001186 [PMID: 20687065 DOI: 10.1002/14651858]

8 **Bacharier LB**, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Götz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills T, Pohunek P, Simons FE, Valovirta E, Wahn U, Wildhaber J. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008; **63**: 5-34 [PMID: 18053013 DOI: 10.1111/j.1398-9995.2007.01586]

9 **Möller C**, Dreborg S, Ferdousi HA, Halken S, Høst A, Jacobsen L, Koivikko A, Koller DY, Niggemann B, Norberg LA, Urbanek R, Valovirta E, Wahn U. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). *J Allergy Clin Immunol* 2002; **109**: 251-256 [PMID: 11842293 DOI: 10.1067/mai.2002.121317]

10 **Akdis CA**. Therapies for allergic inflammation: refining strategies to induce tolerance. *Nat Med* 2012; **18**: 736-749 [PMID: 22561837 DOI: 10.1038/nm.2754]

11 **Calderon MA**, Alves B, Jacobsen M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seaso-

nal allergic rhinitis. *Cochrane Database Syst Rev* 2007; **(1)**: CD001936 [PMID:17253469 DOI: 10.1002/14651858]
12 **Radulovic S**, Calderon MA, Wilson D, Durham S. Sublingual immunotherapy for allergic rhinitis. *Cochrane Database Syst Rev* 2010; (**12**): CD002893 [PMID: 21154351 DOI: 10.1002/14651858]
13 **Compalati E**, Passalacqua G, Bonini M, Canonica GW. The efficacy of sublingual immunotherapy for house dust mites respiratory allergy: results of a GA2LEN meta-analysis. *Allergy* 2009; **64**: 1570-1579 [PMID: 19796205 DOI: 10.1111/j.1398-9995.2009.02129]
14 **Akdis M**, Akdis CA. Mechanisms of allergen-specific immunotherapy: multiple suppressor factors at work in immune tolerance to allergens. *J Allergy Clin Immunol* 2014; **133**: 621-631 [PMID: 24581429 DOI: 10.1016/j.jaci.2013.12.1088]
15 **Larché M**, Akdis CA, Valenta R. Immunological mechanisms of allergen-specific immunotherapy. *Nat Rev Immunol* 2006; **6**: 761-771 [PMID: 16998509 DOI: 10.1038/nri1934]
16 **Francis JN**, Till SJ, Durham SR. Induction of IL-10+CD4+CD25+ T cells by grass pollen immunotherapy. *J Allergy Clin Immunol* 2003; **111**: 1255-1261 [PMID: 12789226 DOI: 10.1067/mai.2003.1570]
17 **Jutel M**, Akdis CA. T-cell regulatory mechanisms in specific immunotherapy. *Chem Immunol Allergy* 2008; **94**: 158-177 [PMID: 18802346 DOI: 10.1159/000155000]
18 **Jutel M**, Van de Veen W, Agache I, Azkur KA, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy and novel ways for vaccine development. *Allergol Int* 2013; **62**: 425-433 [PMID: 24153333 DOI: 10.2332/allergolint.13-RAI-0608]
19 **Moingeon P**, Batard T, Fadel R, Frati F, Sieber J, Van Overtvelt L. Immune mechanisms of allergen-specific sublingual immunotherapy. *Allergy* 2006; **61**: 151-165 [PMID: 16409190 DOI: 10.1111/j.1398-9995.2006.01002]
20 **Mascarell L**, Lombardi V, Louise A, Saint-Lu N, Chabre H, Moussu H, Betbeder D, Balazuc AM, Van Overtvelt L, Moingeon P. Oral dendritic cells mediate antigen-specific tolerance by stimulating TH1 and regulatory CD4+ T cells. *J Allergy Clin Immunol* 2008; **122**: 603-9.e5 [PMID: 18774396 DOI: 10.1016/j.jaci.2008.06.034]
21 **Hamid QA**, Schotman E, Jacobson MR, Walker SM, Durham SR. Increases in IL-12 messenger RNA+ cells accompany inhibition of allergen-induced late skin responses after successful grass pollen immunotherapy. *J Allergy Clin Immunol* 1997; **99**: 254-260 [PMID: 9042055 DOI: 10.1016/S0091-6749(97)70106-4]
22 **Radulovic S**, Jacobson MR, Durham SR, Nouri-Aria KT. Grass pollen immunotherapy induces Foxp3-expressing CD4+ CD25+ cells in the nasal mucosa. *J Allergy Clin Immunol* 2008; **121**: 1467-1472, 1472.e1 [PMID: 18423565 DOI: 10.1016/j.jaci.2008.03.013]
23 **Iliopoulos O**, Proud D, Adkinson NF, Creticos PS, Norman PS, Kagey-Sobotka A, Lichtenstein LM, Naclerio RM. Effects of immunotherapy on the early, late, and rechallenge nasal reaction to provocation with allergen: changes in inflammatory mediators and cells. *J Allergy Clin Immunol* 1991; **87**: 855-866 [PMID: 2013680 DOI: 10.1016/0091-6749(91)90134-A]
24 **Pienkowski MM**, Norman PS, Lichtenstein LM. Suppression of late-phase skin reactions by immunotherapy with ragweed extract. *J Allergy Clin Immunol* 1985; **76**: 729-734 [PMID: 4056258 DOI: 10.1016/0091-6749(85)90679-7]
25 **Jutel M**, Akdis M, Budak F, Aebischer-Casaulta C, Wrzyszcz M, Blaser K, Akdis CA. IL-10 and TGF-beta cooperate in the regulatory T cell response to mucosal allergens in normal immunity and specific immunotherapy. *Eur J Immunol* 2003; **33**: 1205-1214 [PMID: 12731045 DOI: 10.1002/eji.200322919]
26 **Frew AJ**, Powell RJ, Corrigan CJ, Durham SR. Efficacy and safety of specific immunotherapy with SQ allergen extract in treatment-resistant seasonal allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2006; **117**: 319-325 [PMID: 16461133 DOI: 10.1016/j.jaci.2005.11.014]
27 **Passalacqua G**, Durham SR. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. *J Allergy Clin Immunol* 2007; **119**: 881-891 [PMID: 17418661 DOI: 10.1016/j.jaci.2007.01.045]
28 **Walker SM**, Pajno GB, Lima MT, Wilson DR, Durham SR. Grass pollen immunotherapy for seasonal rhinitis and asthma: a randomized, controlled trial. *J Allergy Clin Immunol* 2001; **107**: 87-93 [PMID: 11149996 DOI: 10.1067/mai.2001.112027]
29 **Powell RJ**, Frew AJ, Corrigan CJ, Durham SR. Effect of grass pollen immunotherapy with Alutard SQ on quality of life in seasonal allergic rhinoconjunctivitis. *Allergy* 2007; **62**: 1335-1338 [PMID: 17714551 DOI: 10.1111/j.1398-9995.2007.01455]
30 **Calderon MA**, Casale TB, Nelson HS, Demoly P. An evidence-based analysis of house dust mite allergen immunotherapy: a call for more rigorous clinical studies. *J Allergy Clin Immunol* 2013; **132**: 1322-1336 [PMID: 24139829 DOI: 10.1016/j.jaci.2013.09.004]
31 **Yukselen A**, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Effect of one-year subcutaneous and sublingual immunotherapy on clinical and laboratory parameters in children with rhinitis and asthma: a randomized, placebo-controlled, double-blind, double-dummy study. *Int Arch Allergy Immunol* 2012; **157**: 288-298 [PMID: 22041501 DOI: 10.1159/000327566]
32 **Riechelmann H**, Schmutzhard J, van der Werf JF, Distler A, Kleinjans HA. Efficacy and safety of a glutaraldehyde-modified house dust mite extract in allergic rhinitis. *Am J Rhinol Allergy* 2010; **24**: e104-e109 [PMID: 21244725 DOI: 10.2500/ajra.2010.24.3508]
33 **Pichler CE**, Marquardsen A, Sparholt S, Løwenstein H, Bircher A, Bischof M, Pichler WJ. Specific immunotherapy with Dermatophagoides pteronyssinus and D. farinae results in decreased bronchial hyperreactivity. *Allergy* 1997; **52**: 274-283 [PMID: 9140517 DOI: 10.1111/j.1398-9995.1997.tb00991]
34 **Varney VA**, Edwards J, Tabbah K, Brewster H, Mavroleon G, Frew AJ. Clinical efficacy of specific immunotherapy to cat dander: a double-blind placebo-controlled trial. *Clin Exp Allergy* 1997; **27**: 860-867 [PMID: 9291281 DOI: 10.1111/j.1365-2222.1997.tb01225]
35 **Moline ML**, Pollak CP, Monk TH, Lester LS, Wagner DR, Zendell SM, Graeber RC, Salter CA, Hirsch E. Age-related differences in recovery from simulated jet lag. *Sleep* 1992; **15**: 28-40 [PMID: 1557592 DOI: 10.1111/j.1398-9995.2005.00699]
36 **Penagos M**, Compalati E, Tarantini F, Baena-Cagnani R, Huerta J, Passalacqua G, Canonica GW. Efficacy of sublingual immunotherapy in the treatment of allergic rhinitis in pediatric patients 3 to 18 years of age: a meta-analysis of randomized, placebo-controlled, double-blind trials. *Ann Allergy Asthma Immunol* 2006; **97**: 141-148 [PMID: 16937742 DOI: 10.1016/S1081-1206(10)60004]
37 **Dahl R**, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, Riis B, Grønager PM, Durham SR. Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. *J Allergy Clin Immunol* 2008; **121**: 512-518.e2 [PMID: 18155284 DOI: 10.1016/j.jaci.2007.10.039]
38 **Didier A**, Malling HJ, Worm M, Horak F, Jäger S, Montagut A, André C, de Beaumont O, Melac M. Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis. *J Allergy Clin Immunol* 2007; **120**: 1338-1345 [PMID: 17935764 DOI: 10.1016/j.jaci.2007.07.046]
39 **Bufe A**, Eberle P, Franke-Beckmann E, Funck J, Kimmig M, Klimek L, Knecht R, Stephan V, Tholstrup B, Weisshaar C, Kaiser F. Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy. *J Allergy Clin Immunol* 2009; **123**: 167-173.e7 [PMID: 19130937

DOI: 10.1016/j.jaci.2008.10.044]
40 **Wahn U**, Tabar A, Kuna P, Halken S, Montagut A, de Beaumont O, Le Gall M. Efficacy and safety of 5-grass-pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 2009; **123**: 160-166.e3 [PMID: 19046761 DOI: 10.1016/j.jaci.2008.10.009]
41 **Bergmann KC,** Demoly P, Worm M, Fokkens WJ, Carrillo T, Tabar AI, Nguyen H, Montagut A, Zeldin RK. Efficacy and safety of sublingual tablets of house dust mite allergen extracts in adults with allergic rhinitis. *J Allergy Clin Immunol* 2013: S0091-6749(13)01773-9 [PMID: 24388010 DOI: 10.1016/j.jaci.2013.11.012]
42 **Abramson MJ**, Puy RM, Weiner JM. Is allergen immunotherapy effective in asthma? A meta-analysis of randomized controlled trials. *Am J Respir Crit Care Med* 1995; **151**: 969-974 [PMID: 7697274 DOI: 10.1164/ajrccm/151.4.969]
43 **Abramson MJ**, Puy RM, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2000; **(2)**: CD001186 [PMID: 10796617 DOI: 10.1002/1465185]
44 **Abramson M**, Puy R, Weiner JM. Allergen immunotherapy for asthma. *Cochrane Database Syst Rev* 2003; (**4**):CD001186 [PMID:14583928 DOI: 10.1002/14651858]
45 **García-Robaina JC**, Sánchez I, de la Torre F, Fernández-Caldas E, Casanovas M. Successful management of mite-allergic asthma with modified extracts of Dermatophagoides pteronyssinus and Dermatophagoides farinae in a double-blind, placebo-controlled study. *J Allergy Clin Immunol* 2006; **118**: 1026-1032 [PMID: 17088125 DOI: 10.1016/j.jaci.2006.07.043]
46 **Pifferi M**, Baldini G, Marrazzini G, Baldini M, Ragazzo V, Pietrobelli A, Boner AL. Benefits of immunotherapy with a standardized Dermatophagoides pteronyssinus extract in asthmatic children: a three-year prospective study. *Allergy* 2002; **57**: 785-790 [PMID: 12169173 DOI: 10.1034/j.1398-9995.2002.23498]
47 **Basomba A**, Tabar AI, de Rojas DH, García BE, Alamar R, Olaguíbel JM, del Prado JM, Martín S, Rico P. Allergen vaccination with a liposome-encapsulated extract of Dermatophagoides pteronyssinus: a randomized, double-blind, placebo-controlled trial in asthmatic patients. *J Allergy Clin Immunol* 2002; **109**: 943-948 [PMID: 12063522 DOI: 10.1067/mai.2002.124465]
48 **Blumberga G**, Groes L, Haugaard L, Dahl R. Steroid-sparing effect of subcutaneous SQ-standardised specific immunotherapy in moderate and severe house dust mite allergic asthmatics. *Allergy* 2006; **61**: 843-848 [PMID: 16792582 DOI: 10.1111/j.1398-9995.2006.01088]
49 **Maestrelli P**, Zanolla L, Pozzan M, Fabbri LM. Effect of specific immunotherapy added to pharmacologic treatment and allergen avoidance in asthmatic patients allergic to house dust mite. *J Allergy Clin Immunol* 2004; **113**: 643-649 [PMID: 15100667 DOI: 10.1016/j.jaci.2003.12.586]
50 **Adkinson NF**, Eggleston PA, Eney D, Goldstein EO, Schuberth KC, Bacon JR, Hamilton RG, Weiss ME, Arshad H, Meinert CL, Tonascia J, Wheeler B. A controlled trial of immunotherapy for asthma in allergic children. *N Engl J Med* 1997; **336**: 324-331 [PMID: 9011784 DOI: 10.1056/NEJM199701303360502]
51 **Calderón MA**, Boyle RJ, Penagos M, Sheikh A. Immunotherapy: The meta-analyses. What have we Learned? *Immunol Allergy Clin North Am* 2011; **31**: 159-173, vii [PMID: 21530812 DOI: 10.1016/j.iac.2011.02.002]
52 **Canonica GW,** Bousquet J, Casale T, Lockey RF, Baena-Cagnani CE, Pawankar R, Potter PC, Bousquet PJ, Cox LS, Durham SR, Nelson HS, Passalacqua G, Ryan DP, Brozek JL, Compalati E, Dahl R, Delgado L, van Wijk RG, Gower RG, Ledford DK, Filho NR, Valovirta EJ, Yusuf OM, Zuberbier T. Sub-lingual Immunotherapy. World Allergy Organization Position Paper 2009. *World Allergy Organ J* 2009; **2**: 233-281 [PMID: 20041860 DOI: 10.1002/14651858]
53 **Calamita Z**, Saconato H, Pelá AB, Atallah AN. Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. *Allergy* 2006; **61**: 1162-1172 [PMID: 16942563 DOI: 10.1111/j.1398-9995.2006.01205]
54 **Penagos M**, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, Pedroza A, Canonica GW. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. *Chest* 2008; **133**: 599-609 [PMID: 17951626 DOI: 10.1097/01.WOX.0000301999.54398.13]
55 **Olaguíbel JM**, Alvarez Puebla MJ. Efficacy of sublingual allergen vaccination for respiratory allergy in children. Conclusions from one meta-analysis. *J Investig Allergol Clin Immunol* 2005; **15**: 9-16 [PMID: 15864877]
56 **Pradalier A**, Basset D, Claudel A, Couturier P, Wessel F, Galvain S, André C. Sublingual-swallow immunotherapy (SLIT) with a standardized five-grass-pollen extract (drops and sublingual tablets) versus placebo in seasonal rhinitis. *Allergy* 1999; **54**: 819-828 [PMID: 10485385 DOI: 10.1034/j.1398-9995.1999.00077]
57 **La Rosa M**, Ranno C, André C, Carat F, Tosca MA, Canonica GW. Double-blind placebo-controlled evaluation of sublingual-swallow immunotherapy with standardized Parietaria judaica extract in children with allergic rhinoconjunctivitis. *J Allergy Clin Immunol* 1999; **104**: 425-432 [PMID: 10452766 DOI: 10.1016/S0091-6749(99)70388]
58 **Mosbech H**. Tolerability and efficacy of house dust mite AIT. *Allergy* 2011; **66** Suppl 95: 55-56 [PMID: 21668857 DOI: 10.1111/j.1398-9995.2011.02641]
59 **Marogna M**, Braidi C, Bruno ME, Colombo C, Colombo F, Massolo A, Palumbo L, Compalati E. The contribution of sublingual immunotherapy to the achievement of control in birch-related mild persistent asthma: a real-life randomised trial. *Allergol Immunopathol* (Madr) 2013; **41**: 216-224 [PMID: 23141837 DOI: 10.1016/j.aller.2012.07.004]
60 **Durham SR**, Walker SM, Varga EM, Jacobson MR, O'Brien F, Noble W, Till SJ, Hamid QA, Nouri-Aria KT. Long-term clinical efficacy of grass-pollen immunotherapy. *N Engl J Med* 1999; **341**: 468-475 [PMID: 10441602 DOI: 10.1056/NEJM199908123410702]
61 **Tabar AI**, Arroabarren E, Echechipía S, García BE, Martin S, Alvarez-Puebla MJ. Three years of specific immunotherapy may be sufficient in house dust mite respiratory allergy. *J Allergy Clin Immunol* 2011; **127**: 57-63, 63.e1-3 [PMID: 21211641 DOI: 10.1016/j.jaci.2010.10.025]
62 **Jacobsen L**, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, Koivikko A, Norberg LA, Valovirta E, Wahn U, Möller C. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. *Allergy* 2007; **62**: 943-948 [PMID: 17620073 DOI: 10.1111/j.1398-9995.2007.01451]
63 **Eng PA**, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. *Allergy* 2006; **61**: 198-201 [PMID: 16409196 DOI: 10.1111/j.1398-9995.2006.01011]
64 **Des Roches A**, Paradis L, Menardo JL, Bouges S, Daurés JP, Bousquet J. Immunotherapy with a standardized Dermatophagoides pteronyssinus extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. *J Allergy Clin Immunol* 1997; **99**: 450-453 [PMID: 9111487 DOI: 10.1016/S0091-6749(97)70069-1]
65 **Pajno GB**, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. *Clin Exp Allergy* 2001; **31**: 1392-1397 [PMID: 11591189 DOI: 10.1046/j.1365-2222.2001.01161]
66 **Purello-D'Ambrosio F**, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, Ricciardi L. Prevention of new sensitizations in monosensitized subjects submitted to spe-

cific immunotherapy or not. A retrospective study. *Clin Exp Allergy* 2001; **31**: 1295-1302 [PMID: 11529901 DOI: 10.1046/j.1365-2222.2001.01027]
67 **Inal A**, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. *J Investig Allergol Clin Immunol* 2007; **17**: 85-91 [PMID: 17460946]
68 **Marogna M**, Tomassetti D, Bernasconi A, Colombo F, Massolo A, Businco AD, Canonica GW, Passalacqua G, Tripodi S. Preventive effects of sublingual immunotherapy in childhood: an open randomized controlled study. *Ann Allergy Asthma Immunol* 2008; **101**: 206-211 [PMID: 18727478 DOI: 10.1016/S1081-1206(10)60211-6]
69 **Durham SR**, Emminger W, Kapp A, Colombo G, de Monchy JG, Rak S, Scadding GK, Andersen JS, Riis B, Dahl R. Long-term clinical efficacy in grass pollen-induced rhinoconjunctivitis after treatment with SQ-standardized grass allergy immunotherapy tablet. *J Allergy Clin Immunol* 2010; **125**: 131-138.e1-131-8.e7 [PMID: 20109743 DOI: 10.1016/j.jaci.2009.10.035]
70 **Marogna M**, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Long-lasting effects of sublingual immunotherapy according to its duration: a 15-year prospective study. *J Allergy Clin Immunol* 2010; **126**: 969-975 [PMID: 20934206 DOI: 10.1016/j.jaci.2010.08.030]
71 **Corrigan CJ**, Kettner J, Doemer C, Cromwell O, Narkus A. Efficacy and safety of preseasonal-specific immunotherapy with an aluminium-adsorbed six-grass pollen allergoid. *Allergy* 2005; **60**: 801-807 [PMID: 15876311 DOI: 10.1111/j.1398-9995.2005.00790]
72 **Jutel M**, Jaeger L, Suck R, Meyer H, Fiebig H, Cromwell O. Allergen-specific immunotherapy with recombinant grass pollen allergens. *J Allergy Clin Immunol* 2005; **116**: 608-613 [PMID: 16159631 DOI: 10.1016/j.jaci.2005.06.004]
73 **Bernstein DI**, Epstein T, Murphy-Berendts K, Liss GM. Surveillance of systemic reactions to subcutaneous immunotherapy injections: year 1 outcomes of the ACAAI and AAAAI collaborative study. *Ann Allergy Asthma Immunol* 2010; **104**: 530-535 [PMID: 20568387 DOI: 10.1016/j.anai.2010.04.008]
74 **Bousquet J**, Lockey R, Malling HJ. Allergen immunotherapy: therapeutic vaccines for allergic diseases. A WHO position paper. *J Allergy Clin Immunol* 1998; **102**: 558-562 [PMID: 9802362 DOI: 10.1016/S0091-6749(98)70271-4]
75 **André C**, Fadel R. Anaphylaxis caused by allergen sublingual immunotherapy? *Allergy* 2007; **62**: 1220-1221 [PMID: 17845597 DOI: 10.1111/j.1398-9995.2007.01512]
76 **Dunsky EH**, Goldstein MF, Dvorin DJ, Belecanech GA. Anaphylaxis to sublingual immunotherapy. *Allergy* 2006; **61**: 1235 [PMID: 16942576 DOI: 10.1111/j.1398-9995.2006.01137]
77 **Eifan AO**, Keles S, Bahceciler NN, Barlan IB. Anaphylaxis to multiple pollen allergen sublingual immunotherapy. *Allergy* 2007; **62**: 567-568 [PMID: 17313400 DOI: 10.1111/j.1398-9995.2006.01301]
78 **de Groot H**, Bijl A. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet. *Allergy* 2009; **64**: 963-964 [PMID: 19222420 DOI: 10.1111/j.1398-9995.2009.01998]
79 **Burastero S**. Regarding Gidaro GB, Marcucci F, Sensi L, Incorvaia C, Frati F, Ciprandi G. The safety of sublingual-swallow immunotherapy: an analysis of published studies. *Clin Exp Allergy* 2005; **35**: 1407-1408; author reply 1409 [PMID: 16238803 DOI: 10.1111/j.1365-2222.2005.02366]
80 **Alvarez-Cuesta E**, Bousquet J, Canonica GW, Durham SR, Malling HJ, Valovirta E. Standards for practical allergen-specific immunotherapy. *Allergy* 2006; **61** Suppl 82: 1-20 [PMID: 16930249 DOI: 10.1111/j.1398-9995.2006.01219]
81 **Rodríguez-Pérez N**, Ambriz-Moreno Mde J, Canonica GW, Penagos M. Frequency of acute systemic reactions in patients with allergic rhinitis and asthma treated with sublingual immunotherapy. *Ann Allergy Asthma Immunol* 2008; **101**: 304-310 [PMID: 18814454 DOI: 10.1016/S1081-1206(10)60496-6]
82 **Khinchi MS**, Poulsen LK, Carat F, André C, Hansen AB, Malling HJ. Clinical efficacy of sublingual and subcutaneous birch pollen allergen-specific immunotherapy: a randomized, placebo-controlled, double-blind, double-dummy study. *Allergy* 2004; **59**: 45-53 [PMID: 14674933 DOI: 10.1046/j.1398-9995.2003.00387]
83 **Mungan D**, Misirligil Z, Gürbüz L. Comparison of the efficacy of subcutaneous and sublingual immunotherapy in mite-sensitive patients with rhinitis and asthma--a placebo controlled study. *Ann Allergy Asthma Immunol* 1999; **82**: 485-490 [PMID: 10353581 DOI: 10.1016/S1081-1206(10)62726-3]
84 **Quirino T**, Iemoli E, Siciliani E, Parmiani S, Milazzo F. Sublingual versus injective immunotherapy in grass pollen allergic patients: a double blind (double dummy) study. *Clin Exp Allergy* 1996; **26**: 1253-1261 [PMID: 8955574 DOI: 10.1046/j.1365-2222.1996.d01-280]
85 **Eifan AO**, Akkoc T, Yildiz A, Keles S, Ozdemir C, Bahceciler NN, Barlan IB. Clinical efficacy and immunological mechanisms of sublingual and subcutaneous immunotherapy in asthmatic/rhinitis children sensitized to house dust mite: an open randomized controlled trial. *Clin Exp Allergy* 2010; **40**: 922-932 [PMID: 20100188 DOI: 10.1111/j.1365-2222.2009.03448]
86 **Mauro M**, Russello M, Incorvaia C, Gazzola GB, Di Cara G, Frati F. Comparison of efficacy, safety and immunologic effects of subcutaneous and sublingual immunotherapy in birch pollinosis: a randomized study. *Eur Ann Allergy Clin Immunol* 2007; **39**: 119-122 [PMID: 17523385]
87 **Keles S**, Karakoc-Aydiner E, Ozen A, Izgi AG, Tevetoglu A, Akkoc T, Bahceciler NN, Barlan I. A novel approach in allergen-specific immunotherapy: combination of sublingual and subcutaneous routes. *J Allergy Clin Immunol* 2011; **128**: 808-815.e7 [PMID: 21641635 DOI: 10.1016/j.jaci.2011.04.033]
88 **Tahamiler R**, Saritzali G, Canakcioglu S, Ozcora E, Dirican A. Comparison of the long-term efficacy of subcutaneous and sublingual immunotherapies in perennial rhinitis. *ORL J Otorhinolaryngol Relat Spec* 2008; **70**: 144-150 [PMID: 18391573 DOI: 10.1159/000124286]
89 **Yukselen A**, Kendirli SG, Yilmaz M, Altintas DU, Karakoc GB. Two year follow-up of clinical and inflammation parameters in children monosensitized to mites undergoing subcutaneous and sublingual immunotherapy. *Asian Pac J Allergy Immunol* 2013; **31**: 233-241 [PMID: 24053706 DOI: 10.12932/AP0276.31.3.2013]
90 **Chelladurai Y**, Suarez-Cuervo C, Erekosima N, Kim JM, Ramanathan M, Segal JB, Lin SY. Effectiveness of subcutaneous versus sublingual immunotherapy for the treatment of allergic rhinoconjunctivitis and asthma: a systematic review. *J Allergy Clin Immunol Pract* 2013; **1**: 361-369 [PMID: 24565541 DOI: 10.1016/j.jaip.2013.04.005]
91 **Piazza I**, Bizzaro N. Humoral response to subcutaneous, oral, and nasal immunotherapy for allergic rhinitis due to Dermatophagoides pteronyssinus. *Ann Allergy* 1993; **71**: 461-469 [PMID: 7755664]
92 **El-Qutob D**, Mencia G, Fernandez-Caldas E. Recent advances in immunotherapy for allergic diseases. *Recent Pat Inflamm Allergy Drug Discov* 2014; **8**: 24-35 [PMID: 24237114 DOI: 10.2174/1872213x07666131113111159]
93 **Crameri R**, Flückiger S, Daigle I, Kündig T, Rhyner C. Design, engineering and in vitro evaluation of MHC class-II targeting allergy vaccines. *Allergy* 2007; **62**: 197-206 [PMID: 17298430 DOI: 10.1111/j.1398-9995.2006.01292]
94 **Senti G**, Crameri R, Kuster D, Johansen P, Martinez-Gomez JM, Graf N, Steiner M, Hothorn LA, Grönlund H, Tivig C, Zaleska A, Soyer O, van Hage M, Akdis CA, Akdis M, Rose H, Kündig TM. Intralymphatic immunotherapy for cat allergy induces tolerance after only 3 injections. *J Allergy*

Clin Immunol 2012; **129**: 1290-1296 [PMID: 22464647 DOI: 10.1016/j.jaci.2012.02.026]

95 **Bruzik KS**, Salamonczyk GM, Sobon B. 13C CP-MAS study of the gel phases of 1,2-dipalmitoylphosphatidylcholine. *Biochim Biophys Acta* 1990; **1023**: 143-146 [PMID: 2337426 DOI: 10.1016/j.jaci.2012.10.056]

96 **Senti G**, von Moos S, Tay F, Graf N, Sonderegger T, Johansen P, Kündig TM. Epicutaneous allergen-specific immunotherapy ameliorates grass pollen-induced rhinoconjunctivitis: A double-blind, placebo-controlled dose escalation study. *J Allergy Clin Immunol* 2012; **129**: 128-135 [PMID: 21996342 DOI: 10.1016/j.jaci.2011.08.036]

P- Reviewer: Sahu RP, Wang ZX **S- Editor**: Ji FF **L- Editor**: A **E- Editor**: Lu YJ

Published by **Baishideng Publishing Group Inc**
8226 Regency Drive, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgoffice@wjgnet.com
Help Desk: http://www.wjgnet.com/esps/helpdesk.aspx
http://www.wjgnet.com