APJAI
Asian Pacific Journal of
Allergy and Immunology

REVIEW ARTICLE

Allergen immunotherapy for respiratory allergies in clinical practice: A comprehensive review

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Abstract

Allergen-specific immunotherapy (AIT) is the only treatment that modifies the underlying pathophysiology of IgE-mediated allergic diseases. Evidence shows the efficacy in achieving better control of the symptoms and reduction in medication use in patients with allergic rhinoconjunctivitis and/or asthma. It should be used in association with proper pharmacotherapy for at least three years. The benefits are sustained for several years after discontinuation of treatment. Moreover, it may prevent the development of new sensitization and progression of disease from allergic rhinitis to asthma in children. The favorable efficacy of AIT is associate to the appropriate selection of patients, allergen extracts, adherence, and duration of treatment. Safety during AIT is another concerning issue. AIT has an acceptable safety profile if administered under the appropriate circumstances. Future studies investigating the prescription, efficacy, and safety need to be developed. The new application routes, use of adjuvants, modification of allergens, and use of biologics are currently under evaluation. Moreover, there is an urgent need for real-world data in developing countries regarding the cost-effectiveness analysis, and optimization of AIT schedules and products, so that clinical practice and implementation of AIT for respiratory allergic diseases can be effective and safe.

Key words: Immunotherapy, Allergen, Allergic rhinitis, Asthma, Allergy

Citation:
Lao-Araya, M., Sompornrattanaphan, M., Kanjanawasee, D., Tantilipikorn, P., and the Allergy Asthma and Immunology Association of Thailand (AAIAT) interesting group on immunotherapy. Allergen immunotherapy for respiratory allergies in clinical practice: A comprehensive review. *Asian Pac J Allergy Immunol*. https://doi.org/10.12932/ap-260722-1418

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Introduction

Respiratory allergic diseases, especially allergic rhinitis (AR) and asthma, are among the most frequently encountered non-communicable diseases and significant contributors to the global burden of diseases worldwide. Epidemiological studies have demonstrated that up to 40% of the global population suffer from respiratory allergic diseases.[1,2] The rising trend of respiratory allergies is observed particularly in developing countries. Likewise, population-based surveys using a validated questionnaire conducted in Thai children and adolescents show the prevalence of AR and asthma to be increasing in the past decades.[3,4] The impact of the diseases on patients' health and quality of life has long been recognized, as well as the associated economic burdens.[1,2]

The treatment of respiratory allergic diseases includes patient education, allergen avoidance, pharmacotherapy, and allergen-specific immunotherapy (AIT).[1,2] AIT, repeated allergen administration at regular intervals, has been used as the treatment option for AR since 1911. It is currently the only treatment intervention for IgE-mediated allergic diseases which aims to modify the underlying immunologic mechanisms, ameliorate the diseases, as well as prevent the development of new sensitization and the progression of disease from AR to asthma.[5-10] Although AIT has been considered as an effective treatment modality, the use of AIT in the real-world practice especially in developing countries is still very limited. The potential barriers are its safety, its labor-intensive nature, protracted duration of treatment, high expense, the limited awareness of patients and unfamiliarity with AIT among practitioners.[11]

The aims of this review were to utilize the most current evidence on AIT for the treatment of respiratory allergies to optimize clinical practices and to outline the recommendations for the implementation of an effective and safe use of AIT for respiratory allergic diseases. In addition, we update the relevant topics involved in the administration of AIT for AR and asthma that would help physicians and healthcare providers in clinical practice.

Definition of AIT

AIT refers to the repeated administration of allergen extracts at an effective dose, with regular intervals, for an adequate period. The treatment goal is to modulate immune system, resulting in long-term relief of the allergic symptoms, reduced medication use, and prevention of the development of new allergies. The clinical benefits of AIT persist after discontinuation of the treatment. Even though AIT can be administered in many routes. the standard routes of AIT for respiratory allergies remain as a subcutaneous injection or subcutaneous immunotherapy (SCIT), and sublingually administered as sublingual immunotherapy (SLIT) in either liquid or tablet forms.[5-8,12]

Immunological mechanism of AIT

The allergic immune response begins with the specific allergen being processed by the dendritic cells (DC) or the other antigen-presenting cells (APC) beneath the airway epithelium. Subsequently, these cells present the antigen to the immune system in the nearby lymphoid organs. Type 2 adaptive immune response is stimulated and type 2 cytokines (e.g., IL-4, IL-5, and IL-13) are synthesized and released to allow the production of allergen-specific IgE. This leads to the allergic inflammation and clinical symptoms.[9]

The mechanisms of AIT are complex and still not fully understood. The repeated administration of high-dose allergen extracts leads to the development of immune tolerance which is defined as a decrease in the allergen-specific hypersensitivity. The immune tolerance mechanisms are mainly associated with the induction of regulatory subsets of T and B cells (T reg and B reg), immune deviation in favor of T-helper 1 (Th1) response, and the production of allergen-specific IgG4- and IgA- blocking antibodies. T reg and B reg cells produce TGF-beta, IFN-gamma, and IL-10 which are essential for immunomodulatory activities. These cytokines inhibit the production of type 2 cytokines and histamine release from mast cells and basophils, eosinophilic cationic protein release. Moreover, they facilitate the changes of antibody isotypes in plasma cells to IgG4 and IgA2 instead of IgE and promote immune deviation from Th2 to Th1 cytokine response.[9,13-17] Recently, a novel effector subgroup of T reg cells, follicular regulatory T (Tfr) cells, have been identified to show an increase after AIT. Tfr cells can suppress B-cell activation and antibody production.[16] Existing evidence also suggests the role of AIT in altering innate immunity via innate lymphoid cells type 2 (ILC2) and inducing tolerance.[18-20] Although, skewing of innate and adaptive immune response to a regulatory phenotype is a key event of successful clinical improvement by AIT, the immunological markers which can be consistently correlated with clinical improvements or predictive of long-term tolerance remain elusive.[9]

Clinical efficacy of AIT

Allergic rhinoconjunctivitis (ARC)

Since the first publication of successful SCIT treatment by Noon in 1911, numerous studies have demonstrated that both SCIT and SLIT can significantly improve nasal and ocular symptoms, reduce symptomatic medication usage, and improve the quality of life in ARC patients.[5,6] These data have been evaluated in several meta-analyses and reviews.[21,22] Moreover, there is evidence indicating that these benefits are sustained after treatment discontinuation.[23] A Cochrane meta-analysis which included 51 studies in 2871 patients who were treated with SCIT for seasonal ARC, revealed significant improvements in symptoms severity, quality of life, medication score and immunological parameters.[22] However, the heterogeneity of these SCIT studies existed due to differences in outcome measurements, and variability in the optimal dosage of allergen extracts. In perennial AR, strong evidence of SCIT efficacy appeared primarily in house dust mite (HDM), cockroach and cat allergen extracts.[5,24] The evidence on molds and other furry pets' allergen extracts was limited.[6,7]

The effectiveness of SLIT drops was first reported in a randomized placebo-controlled trial (RCT) in 1982[25] and since then has become a favored approach of AIT with especially high acceptance in Europe due to ease of application and favorable safety profile. The efficacy of SLIT drops remains controversial due to the heterogeneity of its dosing regimen.[6,12] In contrast, SLIT tablets, another formulation of SLIT which uses standardized allergen extracts, has been extensively studied in high-quality, large, and well-designed RCT.[26] The efficacy of SLIT tablets has been established with HDM, grass pollen, ragweed, birch, and Japanese cedar pollen extracts.[12,26,27] When comparing pooled efficacy data from RCTs of SLIT tablets for seasonal and perennial AR to that of pharmacotherapy, SLIT demonstrated comparable overall improvement in total nasal symptom scores to nasal steroid but superior to that of oral antihistamine and antileukotriene.[27]

Nevertheless, comparison between SLIT tablets and pharmacotherapy was singularly disparate, as the SLIT studies allowed use of relief medications, whereas the pharmacotherapy trials usually did not.[26]

Both SCIT and SLIT are effective. However, the lack of any high quality, head-to-head clinical trials means that any definitive knowledge as to their comparative efficacies remains out of reach.[28] However, a recent network meta-analysis suggested a more favorable outcomes of SCIT over SLIT in HDM-AR patients.[29] On the other hand, because of the reported heterogeneity associated with the included studies, the evidence that SCIT is superior to SLIT remains inconclusive.

Local allergic rhinitis

A significant proportion of rhinitis patients who are without systemic IgE-sensitization either through SPT or serum specific IgE still display nasal reactivity upon nasal allergen provocation test. This disease phenotype has been termed local allergic rhinitis (LAR). AR and LAR share many features including type 2 nasal inflammation in the nasal mucosa and secretions, a significant rate of asthma development and the same therapeutic strategies.[30,31] Moreover, a recent systematic review and meta-analysis supported the effectiveness and safety of AIT for LAR. However, its effects were restricted to studies with short-term outcome.[32] Thus, higher-quality studies with longer follow-up periods are required.

Asthma

There is evidence from meta-analyses that AIT could improve short-term symptoms and medication scores in both seasonal- and HDM-allergic asthmatic subjects.[33] Additionally, a few studies showed that SCIT decreased airway hyperresponsiveness, improved quality of life, and had beneficial long-term effects.[33] Large well-designed RCTs which utilized HDM SLIT tablets in HDM-allergic asthmatics demonstrated an improvement in clinical outcomes, ameliorated the risk of exacerbations and reduced the use of inhaled steroid.[34,35] Although these studies included partly controlled, mild-to-moderate asthmatic patients, the HDM SLIT tablets were well tolerated and there were no severe, or fatal adverse reactions. Similarly, a recent systematic review demonstrated that HDM SLIT tablets showed a tendency to effectively reduce inhaled steroid use in adults and adolescents with well, to partly controlled, mild-to-moderate allergic asthma while maintaining a favorable safety profile.[36] This evidence had led the Global Initiative for Asthma (GINA) and the European Academy of Allergy and Clinical Immunology (EAACI) guidelines to recommend the use of HDM SLIT tablets as an add-on therapy for HDM-induced allergic asthma.[37,38] Nevertheless, both SCIT and SLIT have been insufficiently studied in uncontrolled or severe asthma.[36]

Prevention of asthma in AR children

AR is a significant risk factor for development of asthma in children. In an open-label RCT in AR children with birch and/or grass pollen allergy, the treatment with SCIT had a significantly preventive effect on the development of asthma, up-to the 10-year follow-up.[39] In a large well-design double-blind placebo RCT in AR children treated with grass pollen SLIT tablets for 3 years, lower number of children diagnosed with asthma at 2-year after SLIT cessation was shown. Although, the difference was not statistically significant. Meanwhile, there was a significant reduction in the number of asthma symptoms and medication usage in the SLIT treated children.[40] A systematic review concluded that a 3-year AIT treatment also significantly reduced the risk of onset of asthma in children with AR.[41] It is important to note that this strong evidence is shown only on grass and birch pollen allergy. The evidence for HDM AIT, on the other hand, is weaker due to much smaller RCTs.[42]

Prevention of new allergen sensitization

It is well known that the risk of developing new allergic sensitization increases over the years. Several studies reported that patients treated with AIT were less likely to develop new sensitizations, not only during AIT but for several years following completion of the treatment course.[42] A systematic review and meta-analysis demonstrated a protection of new-onset allergen sensitizations within two years after completion of AIT. However long-term preventive effect was not shown compared to the non-AIT group.[41]

Cost effectiveness of AIT

Systematic reviews suggest that AIT is more cost-effective compared to the standard pharmacotherapy in AR patients. Most of these studies were conducted in Europe and the United States, and thus it needed prudent interpretations when applying to developing countries where medical care can be less costly. In Thailand, retrospective studies showed that SCIT was both effective and cost-saving, with an average reduction in treatment cost of 254.2 USD/year.[43,44] However, more well-designed cost-effectiveness studies of AIT in developing countries are required before AIT can be recommended at the national health policy level.

Selection of patients

AIT should be considered as a treatment option in individuals when all of the following conditions[5,6] are met:

- Symptoms suggestive of AR and/or conjunctivitis and/or asthma
- Evidence of IgE sensitization (positive skin prick test (SPT) and/or serum specific IgE) to one or more clinically relevant allergens
- Debilitating symptoms despite appropriate pharmacotherapy and/or allergen avoidance strategies

Other additional benefits of AIT compared to pharmacotherapy alone are the long-term modifications of disease trajectory and prevention of allergic disease progression. AIT may be especially considered in children for its long-term advantages on AR, and the potential to prevent asthma and new sensitizations. Consequently, AIT is also suitable for AR patients whose symptoms are not effectively controlled despite optimal treatment or those who have intolerable adverse reactions to pharmacotherapy. Finally, AIT should always be used in association with appropriate pharmacotherapy and allergen avoidance strategies.[6]

Contraindications for AIT

Absolute contraindications of AIT[5,6,45] are as followed:

- Poorly controlled or uncontrolled asthma (FEV1 < 70% predicted); It should be noted that uncontrolled asthma is the most important risk factor for fatal adverse reactions to AIT. Before prescribing AIT, asthma should be well-controlled or at least partly controlled.
- Severe, active autoimmune diseases
- Active malignancies

The relative contraindications where AIT should only be used with cautions due to higher potential for adverse reactions[6,7,45] are:

- Severe cardiovascular diseases
- Beta-blockers or angiotensin converting enzyme (ACE) inhibitors use; The use of these medicines may increase the risk of severe anaphylaxis and diminish the effect of rescue medications especially adrenaline.
- Severe immunodeficiency: However, HIV-infected patients who have been treated with anti-retroviral drugs and have immune recovery can be treated with AIT.
- Pregnancy: Although there is no evidence on adverse effects of AIT on the fetus or pregnant women, AIT initiation during pregnancy is contraindicated. However, in pregnant women who are in the maintenance phase of AIT and are tolerating the therapy well, AIT can be continued.
- Patients with existing severe psychological barriers such as those with psychiatric problems, mental disabilities or very young children can have compromised communication and understanding of therapy risks and benefits, as well as increased potential for poor adherence.

Allergen selections

Both SPT and serum specific IgE demonstrate high sensitivity and specificity. They are widely used to detect IgE sensitization and are beneficial for the selection of allergens for AIT. Epidemiological studies indicated that most allergic patients are sensitized to more than one allergen (polysensitized), although not all of them may be causing clinical symptoms.[46] Clinical trials with single allergen AIT have shown that polysensitized patients respond as well to AIT as those who are monosensitized.[47] Thus, the selection of allergens for AIT should be consistent with the patient's allergic symptoms as confirmed by history of allergen exposure and relevant IgE sensitization or a positive allergen nasal challenge test.. However, in cases where such selection proves difficult, the use of molecular diagnostic technique, component-resolved determinants (CRD), enables physicians to better determine if patients are, indeed, sensitized to the actual tree and/or grass and/or weed pollen from sensitizations to pollen pan-allergens (e.g., profilin and/or polcalcin).[48] This allows clinicians to confidently prescribe AIT for major allergens even in subjects with multiple allergies. In case of indoor allergen sensitization e.g., dust mite, cockroach, pet's dander, however, the benefit of CRD for selection of allergen in AIT remains unclear.

Successful and safe outcome of AIT depends on the use of high-quality allergen extracts. There are naturally variabilities in allergens' protein amount, antigenicity, and composition. Thus, standardization of allergen extracts is a necessity in controlling the quality, consistency, and reproducibility of their expected efficacies. Although, some of the allergen extracts are standardized, the units and methods for testing the potency in the United States and in European countries are different, thus making meaningful comparisons more difficult.[49] We recommend using standardized AIT products with evidence of efficacy in the clinical documentation of specified total potency or concentration of major allergen when they are available. Additionally, the changing of allergen extract venders between manufacturers is discouraged due to the magnitude of allergen extract inconsistency.[50]

Single- or multiple-allergen AIT, or multiple allergen admixture

Although numerous RCTs and meta-analyses demonstrated the efficacy of single allergen AIT in polysensitized patients, it is common practice in the United States and Thailand that the allergists include multiple allergen extracts to which the patient is sensitized. There are few studies that have investigated the efficacy of multiple allergen SCIT and of these, there are conflicting results.[46] Further well-designed, well-powered RCT supporting the efficacy of multiple allergen AIT is required.[5] Therefore, it is crucial to select only the relevant allergens in AIT.

There are several considerations in case of using multiple allergen admixtures in SCIT[51] which include:

- An effective dose of each allergen must be achieved when delivered in maintenance dose injection.[5]
- Separation of extracts with high proteolytic enzyme activities from other allergens is recommended. Fungal and cockroach extracts have strong proteolytic activity. They should not be mixed with other susceptible allergens.[5,51]
- Allergenic cross-reactivity of allergen should be a concern. The use of CRD can help to differentiate cross-reactivity of major allergens in pollen.[48]

- Using appropriate diluents is encouraged for the stabilization of allergen proteins, prevention of the loss of allergenic potency and disinfection. A phenol-human albumin-saline diluent is well-tolerated and commonly used for making dilution of SCIT extracts.[5]

The evidence of multiple allergen SLITs is scarce. Dual allergen SLITs are reported to be effective when administered separately.[52] The use of multiple allergen admixture in SLIT without the clinical proven is not recommended.

Dose selections

The efficacy of AIT is dependent on achieving a sufficient maintenance dose of each allergen extract.[5] Each SCIT injection should deliver a dose which is considered to be effective for each allergen extract, namely the effective dose. Low doses of AIT are less effective than higher doses, and very low doses may result in a complete loss of efficacy.[5] The recommended effective doses of SCIT allergen extracts reported in clinical trials are shown in **Table 1**. Even though the administration of a greater maintenance dose enhances the likelihood of clinical response, it also increases the risk of severe systemic reactions. According to the preliminary data of ongoing multicenter, randomized, placebo controlled HDM allergen immunotherapy in Thailand, approximately 80% of participants in the active group have reached at least 500 allergy units (AU) of *Dermatophagoides* allergens. On the other hand, some highly sensitive patients may never reach the recommended effective dose due to the risk of systemic reactions. Even then, they might still experience clinical benefits at lower doses.[5] In the case of SLIT, there is no standard recommended SLIT dose in different allergens. We recommend using only the recommended dose based on clinical trials data.

AIT schedules

SCIT generally consists of 2 phases[5,8]:

- Build-up or up-dosing or induction phase; The starting dose is usually at a 1,000-fold dilution of the maintenance concentration. A lesser starting dose can be applied for patients who are highly sensitive, as indicated by the clinical history and skin test reactions. The conventional schedule of SCIT usually consists of weekly increases of allergen extract dosing over a period of a few months, until the maintenance dose is achieved. The build-up phase can be shortened by a clustered or rushed schedule. During the clustered schedule, two or 3 injections are given in one visit and 1-2 visits weekly. The maintenance dose is expected to be reached in just 4-6 weeks. The rushed schedule gives many injections per day on consecutive days, achieving maintenance within a few days. There is conflicting evidence on the reported adverse reaction of rushed schedule. The retrospective analysis and RCT reported that the rate of systemic reactions in clustered compared to conventional schedules did not increase.[53] In contrast, there was a considerable increase in adverse reactions among subjects treated with the rushed regimen, even if pre-medications were prescribed.[54,55]
- Maintenance phase; Once maintenance dose of SCIT is achieved, the injection interval can be increased to 4 weeks. Then, the SCIT should be continued monthly for at least 3 years.

For SLIT, the schedule for administration is dependent upon each product's recommendation. Escalating does may be indicated in SLIT drops. The patients must go through the build-up and maintenance phase like SCIT. On the other hand, there is only one concentration in standard SLIT tablet.

Table 1. Recommended effective doses of SCIT.

Allergen	Probable effective dose range	Probable effective dose range of major allergen
Dust mite: *D. farinae* and *D. pteronyssinus*	500-2,000 AU	7-10 mcg of Der p 1 or Der f 1
Cat hair/ cat pelt	1,000-4,000 BAU	15-17.3 mcg of Fel d 1
Standardized grass	1,000-4,000 BAU	20 mcg of Phl p 5 15 mcg of Doc q 5 and Lol p 5
Bermuda	300-1,500 BAU	NA
Short ragweed	1,000-4,000 AU	6-12 mcg of Amb a 1
Birch	3.28-12 mcg of Bet v1	3.28- 12 mcg of Bet v 1
Dog	15 mcg of Can f1	15 mcg of Can f 1
Nonstandardized extracts: pollen	0.5 mL of 1:100 - 1:200 wt/vol	NA
Nonstandardized extracts: mold/fungi, cockroach	Highest tolerated dose	NA

AU, allergy units; BAU, bioequivalent allergy unit; wt/vol, weight by volume; NA, not available
Adapted from Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011;127(1 Suppl):S1-55.

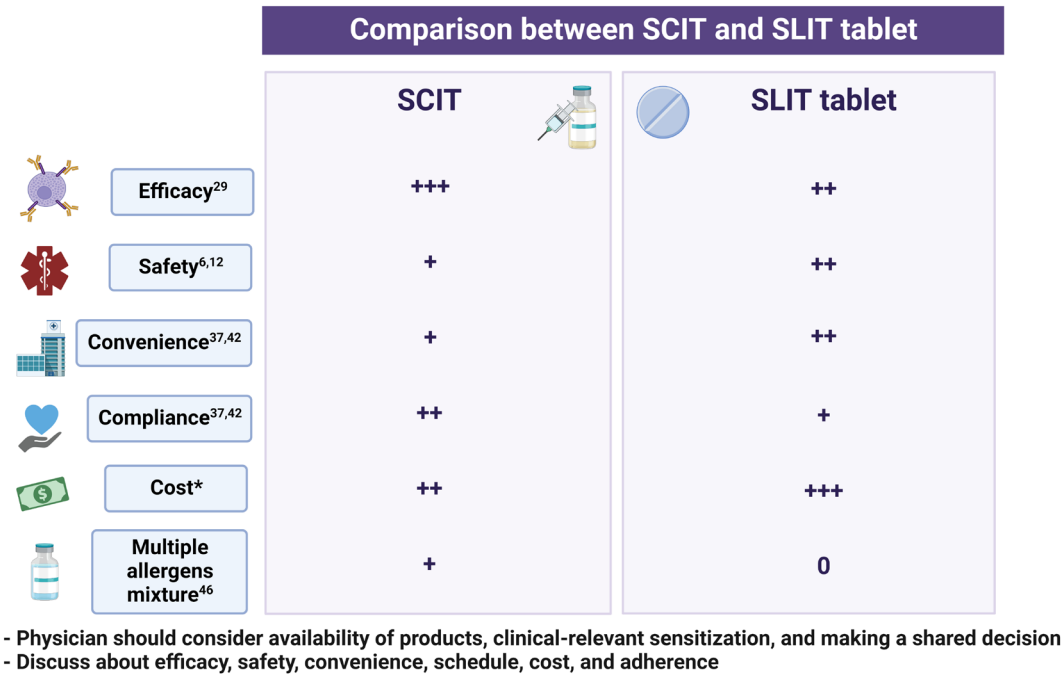

Figure 1. Comparison between SCIT and SLIT.

Abbreviation: SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy

Note: The comparison rating depends on current evidence and experts' opinion.
*The cost of SCIT and SLIT is varied among different countries.

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In such case, daily dosing sublingually without up-dosing is recommended. The effectiveness may depend on the duration of the treatment than the accumulative dose. The comparison between SCIT and SLIT is presented in **Figure 1**.

Safety of AIT

Information regarding the occurrence of systemic and fatal reactions to SCIT was periodically surveyed by the American Academy of Allergy, Asthma, and Immunology (AAAAI). Adverse reactions to SCIT can range from mild local reactions to fatal anaphylaxis. The systematic reactions were reported in 0.1% of all injections given or in 1.9% of patients being treated. There were 2 fatal reactions in 28.9 million injections.[56,57] The risk factors for systemic reactions during SCIT[7,58] are shown in **Table 2**. SCIT should be administered with high caution if these risks are present. In these cases. dosing adjustment should also be considered. During the maintenance phase, if the injection is delayed more than 2 weeks, SCIT dose reduction may be required.[5] The occurrence of large local reactions does not predict subsequent systemic reactions and SCIT dose adjustment is not indicated. However, the occurrence of frequent large local reactions might increase the risk of systemic reactions.[59]

More than 80% of systemic reactions occurred within 30 minutes of administration. And while delayed systemic reactions can occur, they are generally not severe. Regardless, it is prudent that the patients remained under observation in the clinic for at least 30 minutes after SCIT injection.[5,6]

Table 2. Potential risk factors for systemic reactions during AIT.

• Uncontrolled or severe asthma
• High degree of sensitization
• Rapid dose escalation during build-up phase
• Mast cell disease
• Previous systemic reactions to AIT
• Use of beta-blocker, ACE inhibitor
• Changing to a new batch of allergen extract
• Late injection
• Physical stress e.g., high intensity exercise, current infection

In contrast to SCIT, SLIT is considered to be safer because up to 75% of adverse events are local reactions.[6,12] Most of these are self-limited and can present within the oral mucosa such as mouth and throat itchiness or tingling sensations. Mild gastrointestinal adverse events such as mild abdominal discomfort may be reported and can be considered as local reactions if there are no associated systemic symptoms. Most of these local reactions occur in the beginning of the treatment and resolve within a few weeks without any intervention.[26] Severe systemic reactions during SLIT appear much lower than SCIT as well, although fatal anaphylactic reaction from SLIT have been reported. These systemic reactions were usually due to the use of non-standardized allergen extracts, an overdose of an allergen, or a history of severe reactions from SCIT.[60]

Standardized grading systems proposed by the World Allergy Organization (WAO) for reporting AIT systemic adverse events are available and may help clinicians in making treatment decisions if the events do occur.[61]

Administration of AIT and management of adverse reactions

Despite excellent safety and tolerability records of AIT, fatal reactions have occurred. Thus, AIT should be prescribed by an allergy specialist who has experience in AIT treatment. SCIT administration should always be done in a medical setting by experienced healthcare personnel who are trained and certified in the early recognition and management of adverse events, especially that of anaphylaxis. Medical centers or institutions administrating AIT should also be equipped with the necessary instruments as shown in **Table 3**. Regular training of medical personnel on cardiopulmonary resuscitation is required. We recommend that SCIT should be administered only in medical facilities where an observation period of at least 30 minutes after injection is possible, as well as the ability of the healthcare team to promptly recognize and treat anaphylaxis. A longer observation period may be considered in cases where there is a clinical history of delayed systemic reactions.

Table 3. Recommended equipment and medications in venue administrating SCIT.

- Stethoscope and sphygmomanometer
- Tourniquet, syringes, intravenous catheter
- Adrenaline 1:1,000 wt/vol for injection
- Equipment to administer oxygen
- Intravenous fluid set-up and normal saline for infusion
- Antihistamine for injection
- Steroids for injection
- Equipment to maintain an airway
- Pulse oximeter and external defibrillator (optional)
- Bronchodilator (optional)
- Vasopressor drugs (optional)

In patients who experienced adverse events during AIT, pre-treatment with non-sedating antihistamine at least 30-minute before SCIT may be prescribed. This has been shown to be effective in decreasing local reactions, while the effects on systemic reactions remain controversial.[5,6] There are also a few reports on the successful reduction of adverse events such as premedication with montelukast, H2 antihistamine, or adrenaline coated syringe of SCIT extracts.[5,62] Furthermore, omalizumab given in combination with SCIT has been shown to be effective in improving safety, tolerability, and symptom score in highly sensitive allergic asthma patients.[63] If a patient experiences recuring exacerbations related to the course of therapy, it may be necessary to determine whether the continuation of AIT therapy is still warranted.

For administration of SLIT, the first dose should be given under medical supervision in a healthcare facility with a 30-minute observation period. Premedication with antihistamine is not recommended when initiating SLIT because it may mask a potential reaction. Subsequent SLIT dosing can be administered by the patient in the home setting. The patients should also be instructed in recognizing the signs and symptoms of an adverse reaction, as well as determining how and when medical treatment is necessary. SLIT should be temporarily discontinued when extensive inflammation, injury or disruption of oropharyngeal mucosa is present. Significant acute infection or asthma exacerbation also warrant a temporary discontinuation of SLIT. Furthermore, a treatment which has been interrupted for more than 7 days should be reinitiated in a healthcare setting.[12,26]

Although prescribing self-injectable adrenaline or prefilled syringe is not routinely recommended, it should be prescribed in AIT-treated patients who are at high risk of severe systemic reactions such as having a history of anaphylaxis or severe delayed systemic reactions or being highly sensitivity to allergens. It is important to educate these patients on how and when it is appropriate to use self-injectable adrenaline for a severe systemic reaction and when to contact their healthcare providers for support.[64]

Duration and adherence of AIT

The recommended duration of AIT is at least 3 years.[5-7] A study compared the efficacy of 3-year vs 5-year treatment of AIT showed no difference in the overall efficacy. Moreover, 2-year was not long enough to induce the long-term efficacy after AIT discontinuation.[65] There are several placebo-controlled RCTs which demonstrated sustained benefits of a 3-year AIT treatment with a 2-year discontinuation follow-up period. Benefits of AIT can last up to 10 years after discontinuation in one observational study.[23]

Since the success of AIT depends on the duration and adherence to treatment, patients must be informed and properly educated before initiating the treatment in order to obtain the best adherence. The purpose, process, duration, and potential adverse events of AIT must be disclosed, and the informed consent process is mandatory. Adherence rate of SCIT seems to be higher than SLIT because SCIT must be administered by a physician and thus, adherence is easier to monitor. Regular follow-up visits in SLIT patients can improve adherence to the treatment.[66]

In each follow-up visit, the physician should be assessing the effectiveness of AIT by monitoring clinical improvements, rescue medication use, presence of side effects, adherence to treatment schedule and evaluate whether AIT dosing adjustment is required. Currently, there are no laboratory tests or biomarkers that can predict or monitor the efficacy of AIT in clinical settings.[67] The use of clinical symptoms and medication scores are currently the most useful measures in clinical practice.

The improvements of clinical symptoms, reduction in medication use and side effects of AIT are the main reasons to decide if the AIT should be continued. Poor responses to AIT could be due to inappropriate selection or inadequate dosing of allergen, or exposure to high levels of allergens or non-allergic triggers. If clinical improvement is not present after one year in the maintenance phase, cessation of AIT should be considered.[5,6] A summary of the recommendations and an algorithm for effective use of AIT in respiratory allergic diseases are shown in **Table 4** and **Figure 2**.

Unmet needs and the future direction of AIT

The unmet needs for improving the AIT practices are:

- The lack of standardization of allergen products
- The identification of biomarkers as predictors of AIT response
- The development of guidelines on prescribing AIT in polysensitized patients
- The optimization of AIT dosing and schedules
- The investigation of the novel AIT and treatment strategies with improved safety and efficacy

The future direction of AIT is targeting technology that will enhance the efficacy as well as lowering the side effects. These involve the use of specific allergenic peptides, additives or adjuvants, advanced drug delivery systems, and alternative routes of administration. Various routes of AIT administration are available in both injectable and non-injectable forms. The current trend for the route of administration of AIT is toward that of mucosal routes including sublingual, oral, and local nasal.[68,69] These routes are replacing the conventional injection due to their ease of use, requiring no dosage adjustment. In addition, they are less invasive and less labor intensive. Most importantly, immunity triggering through mucosal surface has shown to enhance local mucosal immunity and potentially demonstrates better efficacy than conventional injection. Finally, this trend will overcome some of the unmet needs mentioned earlier.

Even though, both SCIT and SLIT have been acceptance as the standard treatment for respiratory allergies and widely used, AIT prescription in developing countries is very limited due to the scarcity of education, as well as the presence of concerns regarding availability of products, and cost of treatment. To promote the acceptance AIT, studies investigating the efficacy, safety, and cost-effectiveness in the context of developing countries are needed.

Table 4. Summary of AIT in respiratory allergies.

- The treatment goal of AIT is to modulate immune system, resulting in long-term relief of the allergic symptoms, reduce medication use, and prevent the development of new allergies. The clinical benefits of AIT persist after discontinuation of the treatment.
- AIT should be considered in patients with AR and/or conjunctivitis and/or asthma who have IgE sensitization to clinically relevant allergen. The other potential indications are in those patients who do not response sufficiently despite appropriate pharmacotherapy and avoidance strategies, experience unacceptable medication side effects, or wish to avoid long term pharmacotherapy.
- AIT may also be considered in children for its long-term effects on rhinitis, potential to prevent asthma and new sensitization.
- The absolute contraindications of AIT are poorly controlled or uncontrolled asthma (FEV1 < 70% predicted). However, AIT can be used in patients with mild allergic asthma if their asthma is controlled or partly controlled by pharmacotherapy.
- Before initiating AIT, the possible benefits, disadvantages, potential harms, patients' preferences (SCIT or SLIT), patients' adherence to treatment and costs should be discussed with the patient/family on an individual basis.
- Allergens included in AIT should be selected on the results of the relevant IgE- sensitization, associated with consistent allergic symptoms.
- In case of using multiple allergen mixtures in SCIT, the factors that should be considers are an effective dose of each allergen, the proteolytic enzyme activities of allergens, allergenic cross-reactivity, and use of appropriate diluents.
- Standardized AIT products with evidence of efficacy in the clinical documentation should be used when they are available.
- SCIT and SLIT are safe and well-tolerated treatments when they are given by experienced well-trained personnel.
- Severe systemic reactions with SLIT appear to be much lower although the overall rate of any adverse reactions is similar in both SCIT and SLIT.
- SCIT administration:
  - o SCIT should be administered by competent staff, trained to diagnosed symptoms of early systemic reactions or anaphylaxis, with immediate access to resuscitation equipment and a doctor trained in managing anaphylaxis.
  - o Patients must wait in the clinic for at least 30 minutes after a SCIT injection.
  - o Premedication with an antihistamine reduces the frequency and severity of local and systemic cutaneous reactions form SCIT but does not eliminate the risk of other systemic adverse reactions including anaphylaxis.
- SLIT administration:
  - o Patients should wait in clinic for at least 30 minutes after an initial SLIT dosage and staff and equipment should be available to manage any severe local or systemic reaction or anaphylaxis.
  - o Patients receiving SLIT should be informed about how to recognize and manage adverse reactions, particularly severe ones.
- Clinical improvement can be demonstrated after the patient reaches a maintenance dose. If clinical improvement is not apparent after one year of maintenance therapy, discontinuation of AIT should be considered.
- To achieve long-term efficacy, it is recommended that a minimum of three years of therapy is used.
- Currently, there is no biomarkers that will distinguish between patients who will relapse and those who will remain in long-term clinical remission.

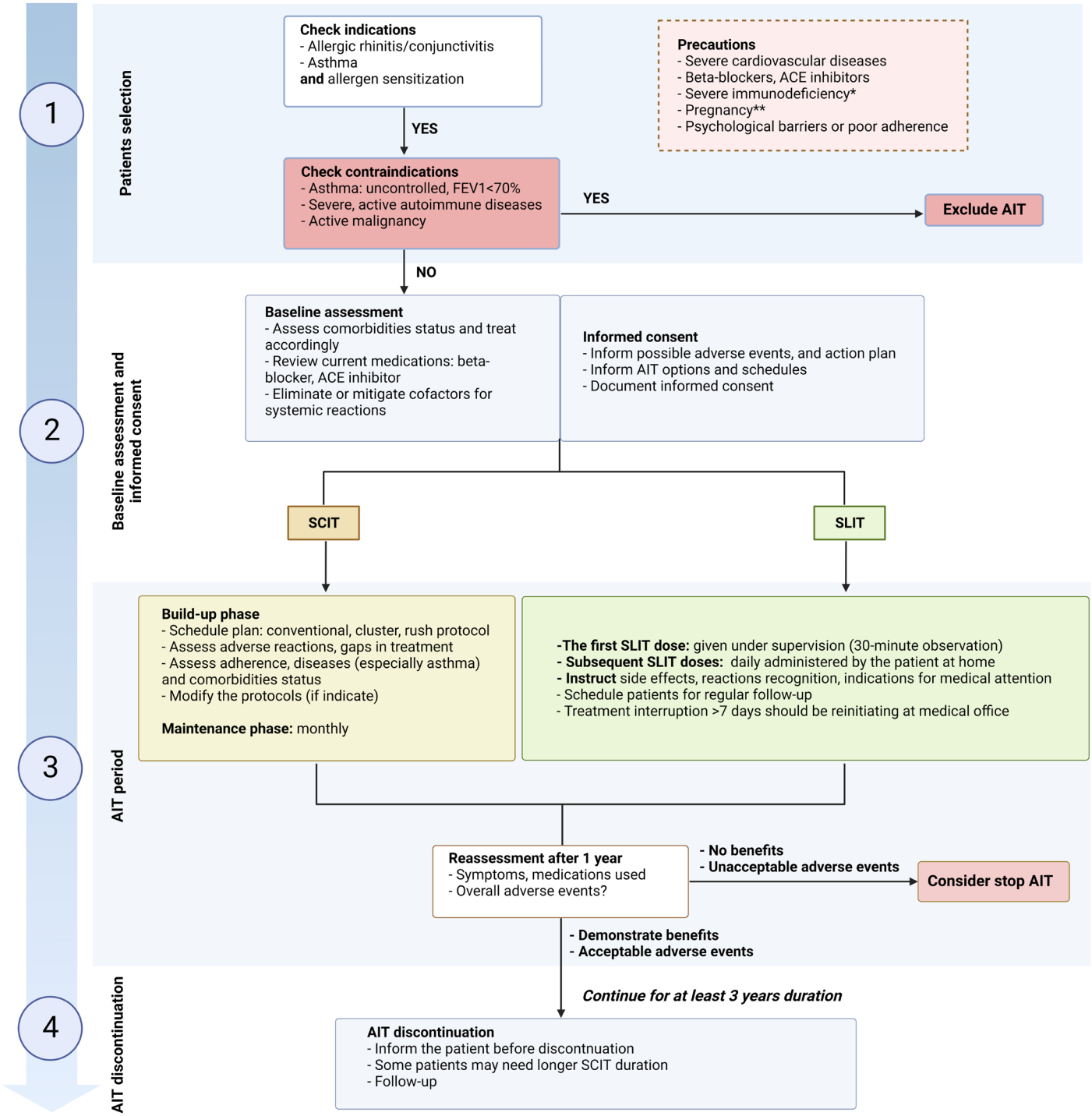

Figure 2. Algorithm for AIT initiation and assessment in respiratory allergies.

Abbreviation: ACE, angiotensin-converting enzyme; AIT, allergen immunotherapy; FEV1, forced expiratory volume in 1 second; HIV, human immunodeficiency virus; SLIT, sublingual immunotherapy; SCIT, subcutaneous immunotherapy

Note: *HIV-infected patients treated with antiretrovirals and have immune recovery, AIT could be considered

**AIT initiation during pregnancy is contraindicated but can be continued if pregnant women are in maintenance phase of AIT.

The figure was created with BioRender.com

Summary

AIT is currently the only etiology-modifying treatment for allergic diseases. It should be considered in patients suffering from allergic rhinoconjunctivitis and/or asthma with a clinically relevant IgE-sensitization. There is strong evidence confirming the efficacy of AIT both during and after the discontinuation of treatment. Moreover, AIT can prevent the development of asthma and new sensitization in children. For long-term benefits, AIT should be prescribed for at least 3 years. Thus, adherence is the key to a successful treatment. Both SCIT and SLIT are well tolerated, but potential severe reactions can occur. Administration of AIT under appropriate clinical settings is critical to ensure the safety.

Acknowledgements

We thank Professor Chulathida Chomchai for her assistance in English editing.

Potential Conflicts of Interest Statement

- ML has received honoraria for scientific lectures from Abbott, A. Menarini, AstraZeneca, GSK, Takeda, Viatris, Organon, Sanofi and Novatis.
- MS has received honoraria for scientific lectures from A. Menarini, AstraZeneca, GSK, Takeda, and Viatris, and research supports from Abbott and Sanofi.
- PS has received honoraria for scientific lectures from A. Menarini, GSK and Viatris, Organon, Sanofi and Novatis, and research supports from Abbott, Sanofi, AstraZeneca.
- DK have no conflict of interest within the scope of the submitted work.

References

1. Bousquet J, Pfaar O, Togias A, Schünemann HJ, Ansotegui I, Papadopoulos NG, et al. 2019 ARIA Care pathways for allergen immunotherapy. Allergy. 2019;74(11):2087-102.
2. Wise SK, Lin SY, Toskala E. International consensus statement on allergy and rhinology: allergic rhinitis-executive summary. Int Forum Allergy Rhinol. 2018;8(2):85-107.
3. Trakultivakorn M, Sangsupawanich P, Vichyanond P. Time trends of the prevalence of asthma, rhinitis and eczema in Thai children-ISAAC (International Study of Asthma and Allergies in Childhood) Phase Three. J Asthma. 2007;44(8):609-11.
4. Chinratanapisit S, Suratannon N, Pacharn P, Sritipsukho P, Vichyanond P. Prevalence and risk factors of allergic rhinitis in children in Bangkok area. Asian Pac J Allergy Immunol. 2019;37(4):232-9.
5. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol. 2011;127(1 Suppl):S1-55.
6. Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI Guidelines on Allergen Immunotherapy: Allergic rhinoconjunctivitis. Allergy. 2018;73(4):765-98.
7. Pfaar O, Bachert C, Bufe A, Buhl R, Ebner C, Eng P, et al. Guideline on allergen-specific immunotherapy in IgE-mediated allergic diseases: S2k Guideline of the German Society for Allergology and Clinical Immunology (DGAKI), the Society for Pediatric Allergy and Environmental Medicine (GPA), the Medical Association of German Allergologists (AeDA), the Austrian Society for Allergy and Immunology (OGAI), the Swiss Society for Allergy and Immunology (SGAI), the German Society of Dermatology (DDG), the German Society of Oto- Rhino-Laryngology, Head and Neck Surgery (DGHNO-KHC), the German Society of Pediatrics and Adolescent Medicine (DGKJ), the Society for Pediatric Pneumology (GPP), the German Respiratory Society (DGP), the German Association of ENT Surgeons (BV-HNO), the Professional Federation of Paediatricians and Youth Doctors (BVKJ), the Federal Association of Pulmonologists (BDP) and the German Dermatologists Association (BVDD). Allergo J Int. 2014;23(8):282-319.
8. Bao Y, Chen J, Cheng L, Guo Y, Hong S, Kong W, et al. Chinese Guideline on allergen immunotherapy for allergic rhinitis. J Thorac Dis. 2017;9(11):4607-50.
9. Boonpiyathad T, Lao-Araya M, Chiewchalermsri C, Sangkanjanavanich S, Morita H. Allergic Rhinitis: What Do We Know About Allergen-Specific Immunotherapy? Front Allergy. 2021;2:747323.
10. Pajno GB, Bernardini R, Peroni D, Arasi S, Martelli A, Landi M, et al. Clinical practice recommendations for allergen-specific immunotherapy in children: the Italian consensus report. Ital J Pediatr. 2017;43(1):13.
11. Sangasapaviliya A, Pholsuwanchai K. Attitude and knowledge of patients with asthma and allergic rhinitis who received allergen immunotherapy in Phramongkutklao Hospital. J Med Assoc Thai. 2010;93 Suppl 6:S100-5.
12. Greenhawt M, Oppenheimer J, Nelson M, Nelson H, Lockey R, Lieberman P, et al. Sublingual immunotherapy: A focused allergen immunotherapy practice parameter update. Ann Allergy Asthma Immunol. 2017;118(3):276-82 e2.
13. van de Veen W, Akdis M. Tolerance mechanisms of allergen immunotherapy. Allergy. 2020;75(5):1017-8.
14. Rattanamanee T, Lumjiaktase P, Kemawichanura N, Kiewgnam P, Jotikasthira W, Manuyakorn W. Regulatory T cell and cytokine changes in children undergoing 3 days rush venom immunotherapy. Asian Pac J Allergy Immunol [Preprint]. 2020 [cited 2022 May 2]. Available from: http://apjai-journal.org/wp-content/uploads/2020/10/AP-140520-0843.pdf
15. Rattanamanee T, Lumjiaktase P, Kemawichanura N, Kiewnga P, Jotikasthira W, Manuyakorn W. Immunologic changes after house dust mite modified rush subcutaneous immunotherapy in allergic rhinitis children. Asia Pac Allergy. 2022;12(1):e4.
16. Boonpiyathad T, Sokolowska M, Morita H, Rückert B, Kast JI, Wawrzyniak M, et al. Der p 1-specific regulatory T-cell response during house dust mite allergen immunotherapy. Allergy. 2019;74(5):976-85.
17. Boonpiyathad T, van de Veen W, Wirz O, Sokolowska M, Rückert B, Tan G, et al. Role of Der p 1-specific B cells in immune tolerance during 2 years of house dust mite-specific immunotherapy. J Allergy Clin Immunol. 2019;143(3):1077-86 e10.
18. Lao-Araya M, Steveling E, Scadding GW, Durham SR, Shamji MH. Seasonal increases in peripheral innate lymphoid type 2 cells are inhibited by subcutaneous grass pollen immunotherapy. J Allergy Clin Immunol. 2014;134(5):1193-5 e4.
19. Mitthamsiri W, Pradubpongsa P, Sangasapaviliya A, Boonpiyathad T. Decreased CRTH2 Expression and Response to Allergen Re-stimulation on Innate Lymphoid Cells in Patients With Allergen-Specific Immunotherapy. Allergy Asthma Immunol Res. 2018;10(6):662-74.
20. Golebski K, Layhadi JA, Sahiner U, Steveling-Klein EH, Lenormand MM, Li RCY, et al. Induction of IL-10-producing type 2 innate lymphoid cells by allergen immunotherapy is associated with clinical response. Immunity. 2021;54(2):291-307 e7.
21. Dhami S, Kakourou A, Asamoah F, Agache I, Lau S, Jutel M, et al. Allergen immunotherapy for allergic asthma: A systematic review and meta-analysis. Allergy. 2017;72(12):1825-48.

22. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev. 2007;(1):CD001936.
23. Penagos M, Durham SR. Duration of allergen immunotherapy for inhalant allergy. Curr Opin Allergy Clin Immunol. 2019;19(6):594-605.
24. Cox L, Calderon M, Pfaar O. Subcutaneous allergen immunotherapy for allergic disease: examining efficacy, safety and cost-effectiveness of current and novel formulations. Immunotherapy. 2012;4(6):601-16.
25. Scadding GK, Brostoff J. Low dose sublingual therapy in patients with allergic rhinitis due to house dust mite. Clin Allergy. 1986;16(5):483-91.
26. Creticos PS. New insights in mite immunotherapy - sublingual tablets. Curr Opin Allergy Clin Immunol. 2021;21(6):602-10.
27. Durham SR, Creticos PS, Nelson HS, Li Z, Kaur A, Meltzer EO, et al. Treatment effect of sublingual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses. J Allergy Clin Immunol. 2016;138(4):1081-8 e4.
28. Durham SR, Penagos M. Sublingual or subcutaneous immunotherapy for allergic rhinitis? J Allergy Clin Immunol. 2016;137(2):339-49 e10.
29. Kim JY, Jang MJ, Kim DY, Park SW, Han DH. Efficacy of Subcutaneous and Sublingual Immunotherapy for House Dust Mite Allergy: A Network Meta-Analysis-Based Comparison. J Allergy Clin Immunol Pract. 2021;9(12):4450-8 e6.
30. Tantilipikorn P, Siriboonkoom P, Sookrung N, Thianboonsong A, Suwanwech T, Pinkaew B, et al. Prevalence of local allergic rhinitis to Dermatophagoides pteronyssinus in chronic rhinitis with negative skin prick test. Asian Pac J Allergy Immunol. 2021;39(2):111-6.
31. Buntarickpornpan P, Veskitkul J, Pacharn P, Visitsunthorn N, Vichyanond P, Tantilipikorn P, et al. The proportion of local allergic rhinitis to Dermatophagoides pteronyssinus in children. Pediatr Allergy Immunol. 2016;27(6):574-9.
32. Hoang MP, Samuthpongtorn J, Chitsuthipakorn W, Seresirikachorn K, Snidvongs K. Allergen-specific immunotherapy for local allergic rhinitis: a systematic review and meta-analysis. Rhinology. 2022;60(1):11-9.
33. Asamoah F, Kakourou A, Dhami S, Lau S, Agache I, Muraro A, et al. Allergen immunotherapy for allergic asthma: a systematic overview of systematic reviews. Clin Transl Allergy. 2017;7:25.
34. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, et al. Efficacy of a House Dust Mite Sublingual Allergen Immunotherapy Tablet in Adults With Allergic Asthma: A Randomized Clinical Trial. JAMA. 2016;315(16):1715-25.
35. Mosbech H, Deckelmann R, de Blay F, Pastorello EA, Trebas-Pietras E, Andres LP, et al. Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: a randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol. 2014;134(3):568-75 e7.
36. Wongsa C, Phinyo P, Sompornrattanaphan M, Krikeerati T, Lumkul L, Thongngarm T. Efficacy and Safety of House Dust Mite Sublingual Immunotherapy Tablet in Allergic Asthma: A Systematic Review of Randomized Controlled Trials. J Allergy Clin Immunol Pract. 2022;10(5):1342-55 e24.
37. Agache I, Lau S, Akdis CA, Smolinska S, Bonini M, Cavkaytar O, et al. EAACI Guidelines on Allergen Immunotherapy: House dust mite-driven allergic asthma. Allergy. 2019;74(5):855-73.
38. Ish P, Malhotra N, Gupta N. GINA 2020: what's new and why? J Asthma. 2021;58(10):1273-7.
39. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007;62(8):943-8.
40. Valovirta E, Petersen TH, Piotrowska T, Laursen MK, Andersen JS, Sørensen HF, et al. Results from the 5-year SQ grass sublingual immunotherapy tablet asthma prevention (GAP) trial in children with grass pollen allergy. J Allergy Clin Immunol. 2018;141(2):529-38 e13.
41. Kristiansen M, Dhami S, Netuveli G, Halken S, Muraro A, Roberts G, et al. Allergen immunotherapy for the prevention of allergy: A systematic review and meta-analysis. Pediatr Allergy Immunol. 2017;28(1):18-29.
42. Halken S, Larenas-Linnemann D, Roberts G, Calderón MA, Angier E, Pfaar O, et al. EAACI guidelines on allergen immunotherapy: Prevention of allergy. Pediatr Allergy Immunol. 2017;28(8):728-45.
43. Thanborisutkul K, Khodtecha N, Kulalert P, Sritipsukho P, Poachanukoon O, Nanthapisal S. Efficacy, patients' perception, and cost of medication in allergic rhinitis with subcutaneous immunotherapy. Asian Pac J Allergy Immunol [Preprint]. 2020 [cited 2022 May 2]. Available from: http://apjai-journal.org/wp-content/uploads/2020/08/AP-040320-0781.pdf
44. Pothirat C, Chaiwong W. A Real-World Effectiveness of Subcutaneous Immunotherapy on the Cost of Medication, Allergic Rhinitis, and Asthma Exacerbations, as well as Upper Respiratory Tract Infection in Subjects with Allergic Rhinitis with or without Asthma: A Retrospective Pilot Study. Medicina (Kaunas). 2021;57(11):1229.
45. Pitsios C, Tsoumani M, Bilo MB, Sturm GJ, Rodríguez Del Río P, Gawlik R, et al. Contraindications to immunotherapy: a global approach. Clin Transl Allergy. 2019;9:45.
46. Demoly P, Passalacqua G, Pfaar O, Sastre J, Wahn U. Management of the polyallergic patient with allergy immunotherapy: a practice-based approach. Allergy Asthma Clin Immunol. 2016;12:2.
47. Nelson H, Blaiss M, Nolte H, Wurtz SO, Andersen JS, Durham SR. Efficacy and safety of the SQ-standardized grass allergy immunotherapy tablet in mono- and polysensitized subjects. Allergy. 2013;68(2):252-5.
48. Barber D, Diaz-Perales A, Escribese MM, Kleine-Tebbe J, Matricardi PM, Ollert M, et al. Molecular allergology and its impact in specific allergy diagnosis and therapy. Allergy. 2021;76(12):3642-58.
49. Bonertz A, Roberts G, Slater JE, Bridgewater J, Rabin RL, Hoefnagel M, et al. Allergen manufacturing and quality aspects for allergen immunotherapy in Europe and the United States: An analysis from the EAACI AIT Guidelines Project. Allergy. 2018;73(4):816-26.
50. Bonertz A, Roberts GC, Hoefnagel M, Timon M, Slater JE, Rabin RL, et al. Challenges in the implementation of EAACI guidelines on allergen immunotherapy: A global perspective on the regulation of allergen products. Allergy. 2018;73(1):64-76.
51. Esch RE. Allergen immunotherapy: what can and cannot be mixed? J Allergy Clin Immunol. 2008;122(3):659-60.
52. Fujii T, Kitamura Y, Kamimura S, Ishitani K, Takeda N. Efficacy of dual sublingual immunotherapy with Japanese cedar pollen and house dust mite allergens in patients with allergic rhinitis sensitized to multiple allergens. Laryngoscope Investig Otolaryngol. 2022;7(1):36-42.
53. Tabar AI, Echechipia S, Garcia BE, Olaguibel JM, Lizaso MT, Gómez B, et al. Double-blind comparative study of cluster and conventional immunotherapy schedules with Dermatophagoides pteronyssinus. J Allergy Clin Immunol. 2005;116(1):109-18.
54. Winslow AW, Turbyville JC, Sublett JW, Sublett JL, Pollard SJ. Comparison of systemic reactions in rush, cluster, and standard-build aeroallergen immunotherapy. Ann Allergy Asthma Immunol. 2016;117(5):542-5.
55. Manuyakorn W, Benjaponpitak S, Kamchaisatian W, Sasisakulporn C, Jotikasthira W. Safety and efficacy of ant rush immunotherapy in children. Asian Pac J Allergy Immunol. 2017;35(3):156-60.
56. Epstein TG, Liss GM, Murphy-Berendts K, Bernstein DI. AAAAI/ACAAI surveillance study of subcutaneous immunotherapy, years 2008-2012: an update on fatal and nonfatal systemic allergic reactions. J Allergy Clin Immunol Pract. 2014;2(2):161-7.
57. Epstein TG, Liss GM, Berendts KM, Bernstein DI. AAAAI/ACAAI Subcutaneous Immunotherapy Surveillance Study (2013-2017): Fatalities, Infections, Delayed Reactions, and Use of Epinephrine Autoinjectors. J Allergy Clin Immunol Pract. 2019;7(6):1996-2003 e1.
58. Calderon MA, Vidal C, Rodriguez Del Rio P, Just J, Pfaar O, Tabar AI, et al. European Survey on Adverse Systemic Reactions in Allergen Immunotherapy (EASSI): a real-life clinical assessment. Allergy. 2017;72(3):462-72.
59. Roy SR, Sigmon JR, Olivier J, Moffitt JE, Brown DA, Marshall GD. Increased frequency of large local reactions among systemic reactors during subcutaneous allergen immunotherapy. Ann Allergy Asthma Immunol. 2007;99(1):82-6.
60. Calderon MA, Simons FE, Malling HJ, Lockey RF, Moingeon P, Demoly P. Sublingual allergen immunotherapy: mode of action and its relationship with the safety profile. Allergy. 2012;67(3):302-11.
61. Cox L, Larenas-Linnemann D, Lockey RF, Passalacqua G. Speaking the same language: The World Allergy Organization Subcutaneous Immunotherapy Systemic Reaction Grading System. J Allergy Clin Immunol. 2010;125(3):569-74.

62. Sapsaprang S, Boonard K, Pacharn P, Srisuwatchari W, Visitsunthorn N, Jirapongsananuruk O. Epinephrine-coated syringe for SCIT reduced local reactions: A randomized, double-blind, placebo-controlled trial. J Allergy Clin Immunol Pract. 2020;8(4):1465-7 e1.
63. Dantzer JA, Wood RA. The use of omalizumab in allergen immunotherapy. Clin Exp Allergy. 2018;48(3):232-40.
64. Bernstein D, Tankersley M, Russell H. Controversies in Allergy: Injectable Epinephrine Should Be Prescribed to All Patients on Subcutaneous Aeroallergen Immunotherapy. J Allergy Clin Immunol Pract. 2020;8(4):1211-5.
65. Scadding GW, Calderon MA, Shamji MH, Eifan AO, Penagos M, Dumitru F, et al. Effect of 2 Years of Treatment With Sublingual Grass Pollen Immunotherapy on Nasal Response to Allergen Challenge at 3 Years Among Patients With Moderate to Severe Seasonal Allergic Rhinitis: The GRASS Randomized Clinical Trial. JAMA. 2017;317(6):615-25.
66. Leader BA, Rotella M, Stillman L, DelGaudio JM, Patel ZM, Wise SK. Immunotherapy compliance: comparison of subcutaneous versus sublingual immunotherapy. Int Forum Allergy Rhinol. 2016;6(5):460-4.
67. Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. Allergy. 2017;72(8):1156-73.
68. Kanjanawasee D, Tantilipikorn P. LNIT-Local nasal immunotherapy in allergic rhinitis: revisited evidence and perspectives. Curr Opin Allergy Clin Immunol. 2022;22(4):259-67.
69. Kasemsuk N, Ngaotepprutaram P, Kanjanawasee D, Suwanwech T, Durham SR, Canonica GW, et al. Local nasal immunotherapy for allergic rhinitis: A systematic review and meta-analysis. Int Forum Allergy Rhinol [Preprint]. 2022 [cited 2022 May 11]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/alr.23011