ASTHMA ALLERGY IMMUNOLOGY
ASTIM ALLERJİ İMMÜNOLOJİ

doi: 10.21911/aai.652
Asthma Allergy Immunol 2021;19:156-165

RESEARCH ARTICLE

Received: 29.05.2021 • Accepted: 31.08.2021
Online Published: 18.11.2021

Standardized Quantitative Evaluation of Clinical Effectiveness and Side Effect Profile of Subcutaneous and Sublingual Allergen-Specific Immunotherapy in Children: A 5-Year Single Center Experience

Nazan TÖKMECİ[1], Ali DEMİRHAN[1], Merve TURKEGUN SENGUL[2], Burcu CAGLAR YUKSEK[1], Aylin KONT ÖZHAN[1], Tuğba ARIKOĞLU[1], Semanur KUYUCU[1]

[1] Department of Pediatric Allergy and Immunology, Mersin University School of Medicine, Mersin, Turkey
[2] Department of Biostatistics, Mersin University School of Medicine, Mersin, Turkey

Corresponding Author: Nazan Tökmeci ✉ ntokmeci@hotmail.com

ABSTRACT

Objective: Allergen-specific immunotherapy (allergen-SIT) is a treatment method with variable efficacy in allergic diseases. This study aimed to investigate the effectiveness of allergen immunotherapy, frequency of LRs and SRs and variables affecting these parameters in patients who underwent allergen-SIT.

Materials and Methods: In this study, the recorded data of 81 patients, who received subcutaneous (SCIT) or sublingual (SLIT) allergen immunotherapy for respiratory allergic diseases between 2014 and 2019, were analyzed. In asthma and/or allergic rhinoconjunctivitis (ARC) patients, the effectiveness of treatment was evaluated by analysing the change rates in disease symptom, medication and combined scores (symptom + medication) and visual analog score (VAS). Treatment success was defined by the degree of decrease in scores as; high response above 50%; low response between 20-50%; and failure <20%.

Results: The mean age of allergen-SIT initiation was 11.4± 3.1 years. Diagnostic distributions of the patients were asthma (± ARC) in 64.2%, and ARC (without asthma) in 35.8%. The mode of allergen-SIT was SCIT in 77.8% (65% asthma and 35% ARC) and SLIT in 22.2% (61.1% asthma and 38.9% ARC). The main allergens used in allergen-SIT were mite (79%), grass-grain pollen (33.3%), alternaria (9.9%) and olea (8.6%). There was a significant decrease in symptoms, medication, combined and VAS scores in the asthma and ARC groups ($p < 0.0001$), when end-SCIT values were compared to baseline. SLIT also resulted in significant decreases in these scores except asthma medication score. Among the asthma patients the rate of high-responders was 88.8% by SCIT and 50% by SLIT, according to combined asthma score. Among the ARC (without asthma) patients the rate of high-responders was 100% for both SCIT and SLIT. SCIT resulted in local (LR) and systemic side effects (SR) in 18% and 0.6% (all Grade I and Grade II) of the total injections performed. A high number of total injections was significantly associated with higher LR and SR rates. While LR was observed in 16.6% of the patients who underwent SLIT, no systemic reaction was found in any of the patients.

Conclusion: SCIT was highly successful in the treatment of asthma and ARC in terms of the degree of therapeutic response. SLIT resulted in a high rate of good response in ARC patients, but a lower response degree in asthmatic patients. Systemic side effects were very low as a result of close risk monitoring and the dose adjustments performed.

Keywords: Allergen-specific immunotherapy, SCIT, SLIT, efficacy, symptom score, medication score, visual analog score, side effects

INTRODUCTION

Allergen-specific immunotherapy (allergen-SIT), the only disease-modifying treatment option for patients with IgE-mediated allergic rhinitis and allergic asthma, has been used in clinical practice for decades (1). Since the notification of allergic rhinitis treatment with subcutaneous immunotherapy (SCIT) using pollen extracts by Noon and Freeman in 1911, significant advances have been made in terms of allergen-SIT efficacy and safety (2,3). The first randomized study on sublingual immunotherapy (SLIT)

ORCID Nazan Tökmeci / 0000-0002-8489-8772, Ali Demirhan / 0000-0003-3107-4873, Merve Turkegun Sengul / 0000-0002-4405-521X, Burcu Caglar Yuksek / 0000-0002-3540-713X, Aylin Kont Özhan / 0000-0003-0486-0422, Tuğba Arıkoğlu / 0000-0003-3340-571X, Semanur Kuyucu / 0000-0003-1999-6496

was conducted by Scadding in 1986 (4). Placebo-controlled studies performed with allergen-SIT in the following years led to the emergence of scientific evidence for both allergic rhinitis/rhinoconjunctivitis (AR/ARC) and asthma to improve symptoms and reduce drug use (5, 6).

Side effects can be seen with both SCIT and SLIT treatment. Although the benefits of SCIT treatment are very clear, the occurrence of local and especially systemic side effects limit its use. Side effects that occur with SCIT range from local reactions (LRs) to severe systemic reactions (SRs) such as anaphylaxis and are classified with a grading system by the American Academy of Allergy, Asthma and Immunology (AAAAI) (7). Studies have shown that LRs are common in SLIT treatment, and these side effects are often in the form of local itching and edema in the oral cavity and throat that can last for weeks (8). Increasing knowledge about the efficacy and side effects of SCIT and SLIT treatments will enable us to use it in the right indications in patients with asthma and ARC in allergy practice, and to predict the risk of side effects, especially systemic side effects that limit the use of SIT, making, our risk management will be more effective.

In this study, we aimed to evaluate the efficacy of SCIT and SLIT treatments in patients with asthma and ARC with standardized qualitative scoring systems and lung function indices, and also to reveal the side effect profiles.

MATERIAL and METHODS

Patient Population

In this study, the recorded data including demographic and clinical characteristics, lung function and laboratory tests of 81 patients who had undergone SCIT (Allergopharma [Germany], ALK-Abello [Spain] and Stallergens [France] standardized allergen extracts) and SLIT (Stallergens [France]) due to asthma and/or ARC between 2014-2019 were analyzed. Allergen-SIT was performed in the patients diagnosed with mild-moderate asthma and moderate-severe ARC. Although SLIT was the preferred method in monosensitized ARC (without asthma) patients and SCIT in polysensitized asthmatic patients, the choice of SCIT or SLIT treatment was made by considering patient compliance and the family's request in most cases. Immunotherapy initiation age and duration, type, allergen content and number, adjuvant content, number of injections, and local and systemic side effect parameters were also evaluated. Recorded symptom and medication scores and visual analog scale (VAS) values of the patients before, and at the middle and end of allergen-SIT were calculated.

Scoring Methods

A clinical scoring method (9) and VAS scoring method (10) were used for the quantitative evaluation of clinical improvements.

Allergic Rhinoconjunctivitis (ARC) Symptom Score; Allergic nasal symptoms were evaluated over four clinical symptoms: nasal obstruction, nasal itching, sneezing and nasal discharge. Allergic conjunctival symptoms were evaluated on the basis of two clinical symptoms as watery eyes and itching/redness.

Asthma Symptom Score; was evaluated on four clinical symptoms: cough, shortness of breath, wheezing, and chest tightness.

A four-point grading of symptom scores was made and for each symptom, as 0 = no symptoms, 1 = mild symptoms, 2 = moderate symptoms, and 3 = severe symptoms.

Drug Score; Drug scores were calculated by evaluating the drugs used by the patients to control their symptoms: oral, ocular or intranasal antihistamines were scored as 1 point inhaled beta 2 agonist bronchodilators when needed as 1 point, intranasal corticosteroids as 2 points, inhaled corticosteroids as 2 points, and oral corticosteroids as 3 points. The highest score received by the patient was calculated as the drug score.

Combined Score; This was calculated by taking the mean of the sum of the symptoms and medication scores.

Visual Analog Score; 0 points were graded as no symptoms, 100 points as severe symptoms. The patients were asked to score the severity of their allergic symptoms between 0 and 100, and VAS scores were calculated.

Baseline, mid-treatment and end-treatment symptom scores, drug scores, combined scores and visual analog scores of the patients were calculated and the changes in scores over the years were compared statistically.

Treatment Response Definition; Patients with a combined score reduction rate over 50% were defined as high response; between 20-50% as low response; and <20% as failure (11).

Laboratory Follow-Ups

In order to evaluate the effectiveness of treatment in patients diagnosed with asthma and/or ARC and who completed their treatment, post-treatment values of total IgE, peripheral eosinophil count, spirometric parameters including forced expiratory volume in 1 s (FEV)%, forced vital capacity (FVC), the ratio FEV1/FVC, peak expiratory flow (PEF)%, maximum mid-expiratory flow (MMEF)%, the presence of FEV1 reversibility (≥ 12% or ≥ 200 ml after 200-400 mcg salbutamol inhalation), the presence of MMEF reversibility (> 30% after 200-400 mcg salbutamol inhalation), and PC20 (the concentration of methacholine that causes a 20% decrease in FEV1) values in methacholine provocation tests were compared to the baseline.

Evaluation of Side Effects

Side effects in patients with allergen-SIT were classified as LRs and SRs. The reactions occurring within the first 30 minutes were evaluated as early reactions, and the reactions occurring after 30 minutes as late reactions (12). LRs were defined as pruritus, edema and/or erythema at the injection site for SCIT application (12) and local itching and swelling of the mouth, lips and tongue, irritation in the throat, nausea, abdominal pain, vomiting, diarrhea, and uvula edema in patients who underwent SLIT (13). SRs were classified according to the Rating System of The World Allergy Organization (WAO) (7); Grade I: Reactions localised in a single organ including the skin (as pruritus, urticaria flushing or mild angioedema), upper respiratory tract (rhinitis, throat clearing or cough) or conjunctivisa, Grade II: Signs of more than one organ system present or lower respiratory symptoms (as asthma [eg, less than 40% PEF or FEV1 drop, responding to an inhaled bronchodilator]) or gastrointestinal symptoms (abdominal cramps, vomiting or diarrhea) , Grade III: Lower respiratory symptoms (as asthma [eg, 40%, PEF or FEV1 drop NOT responding to an inhaled bronchodilator]) or upper respiratory symptoms (laryngeal uvula, or tongue edema with or without stridor), Grade IV: Severe lower or upper respiratory symptoms the presence of respiratory failure) or cardiovascular symptoms (hypotension with or without loss of consciousness), Grade V: Death.

Consent forms were signed by all patients before initiating SIT. The study was approved by the Clinical Research Ethics Committee of Mersin University (date: 24.06.2020, number: 2020 /438

Statistical Method

STATISTICA version 13.5.0.17 was used for statistical analysis of the data. The normal distribution assumption was checked with the Shapiro-Wilk test. Categorical variables are summarized with number (n) and percentage (%) values, continuous variables that satisfy the normal distribution condition are summarized with mean ± standard deviation, minimum and maximum, and those that do not satisfy the normal distribution are summarized with median, 25^{th} and 75^{th} quartile values. Chi-square test or Fisher's exact test was used to investigate the relationships between categorical variables. The mean values of the two groups were compared with the Student-t test and the medians with the Mann Whitney U test. The Friedman test was used to compare symptom, medication and VAS measurements before, during, and after allergen-SIT. Wilcoxon and Paired T-tests were used to compare total IgE, peripheral eosinophil count, spirometric indices and PC20 values before and after allergen-SIT. Multivariate logistic regression analysis (MLR) was performed to determine risk factors that are significant on side effects and treatment efficiency. Variables with $p<0.25$ according to the univariate test results were included in the MLR model as possible risk factors. Odds ratios and 95% confidence intervals of odds ratios were calculated. Statistical significance level (p) was taken as <0.05 for all comparisons.

RESULTS

Eighty-one patients with respiratory allergies who underwent allergen-SIT treatment between 2014 and 2019 were evaluated. Forty-six (56.8%) of the patients were male. The mean age at diagnosis of relevant allergic disease was 8.9 ± 3.6 years and the mean age of onset of allergen-SIT was found to be 11.4 ± 3.1 years. The diagnostic distribution of the patients was asthma (± ARC) in 64.2%, and only ARC (without asthma) in 35.8%. Among asthmatic patients 92.3% had accompanying ARC. The median duration of allergen-SIT application was found to be 3.7 (2.1-4.6) years.

The mode of allergen-SIT was SCIT in 77.8% and SLIT in 22.2% of the patients. The number of allergens given to the patients during allergen-SIT was one allergen in 58%, two allergens in 13.6%, and three or more allergens in 28.4%. The distribution of allergens in SIT content was mainly mite 79%, grass-grain pollen 33.3%, alternaria 9.9%, and olea 8.6%. The adjuvant content in SCIT was

aluminum hydroxide in 69.8% and calcium phosphate in 30.2% of the patients (Table I).

In SCIT sessions, 69.8% (n=44) of the patients received one injection and 30.2% (n=19) had two injections. A total of 4567 injections were applied and LRs emerged in 18% (n=823), and SRs in 0.6% (n=28) of the total injections (Table II). While 36.2% (n=308) of all side effects (LRs and SRs) were observed in the build-up phase, 63.8% (n=543) were observed in the maintenance phase of the treatment.

Table I: Clinical and treatment characteristics of SIT patients.

Gender, male, n (%)	46 (56.8)
Age at diagnosis (year) (mean±SD)	8.9 ± 3.6
Duration of pre-SIT follow-up (years) median (Q_1-Q_3)	2.2 (0.7-4.1)
Allergen-SIT initiation age (years) (Mean±SD)	11.4 ± 3.1
Duration of allergen-SIT (years) Median (Q_1-Q_3)	3.7 (2.1- 4.6)
Underlying disease indicated for allergen-SIT, n (%)	
ARC without asthma	29 (35.8)
Asthma ±ARC	52 (64.2)
Accompanying other allergic disease, n (%)	
Food allergy	3 (3.7)
Atopic dermatitis	9 (11.1)
Peripheral eosinophil count (/mm^3) Median (Q_1-Q_3)	355 (210-610)
Serum total IgE (IU/L) Median (Q_1-Q_3)	549 (157-1045)
Mode of allergen-SIT, n (%)	
SCIT	63 (77.8)
SLIT	18 (22.2)
Number of allergens included in SIT, n (%)	
Single allergen	47 (58.0)
Two allergens	11 (13.6)
Three or more allergens	23 (28.4)
SIT allergen content, n (%)	
Mite	64 (79.0)
Grass-grain mixture	27 (33.3)
Alternaria	8 (9.9)
Olea	7 (8.6)
Weed	3 (3.7)
Allergen-SIT adjuvant ingredient, n (%)	
Aluminium hydroxide	44 (69.8)
Calcium phosphate	19 (30.2)

ARC: Allergic rhinoconjunctivitis, **SPT:** Skin prick test, **Allergen-SIT:** Allergen-specific immunotherapy, **SCIT:** Subcutaneous IT, **SLIT:** Sublingual IT.

Distribution of the side effects according to chronology revealed that 71.4% (n=608) of LRs and 1.5% (n=13) of SRs were early onset reactions. The distribution of SRs according to grades showed that all were Grade I or Grade 2 reactions. (Table II). SLIT resulted in LRs in 16.6% (n=3) of the patients, no SRs was observed. The patients who underwent SCIT were evaluated in terms of parameters affecting the occurrence of LR and SR. The effects of gender, diagnostic category, age of diagnosis, age of onset of allergen-SIT, number and type of allergens included in allergen-SIT, allergen-SIT adjuvant content, total number of given injections, and number of injections applied in each session on side effect development were investigated by regression analysis. In multivariate logistic regression analysis (MLR), only the total number of injections was found to increase the risk of LR (p=0.01, OR: 1.03, 95% Cl: 1.01-1.05) and SR (p=0.04, OR: 1.01, 95% Cl: 1.01-1.03).

Laboratory parameters and spirometric indices of SCIT and SLIT patients were compared at the beginning and end of the treatment. A decrease in mean values of peripheral eosinophil count (p=0.024), and increase in mean values of MMEF% (p=0.021) were found to be statistically significant while serum total IgE, FEV1%, FEV1/ FVC, PEF, FEV1 reversibility, MMEF reversibility and methacoline PC20 values did not show any significant change (p>0.05) in the SCIT patients. In the SLIT group, only PEF (p=0.006), increased significantly, while there were no significant differences in the other spirometric and other laboratory indices (data not shown).

Table II: Side effect profile of SCIT injections.

	Local reactions	**Systemic reactions**
Total number of injections (n=4567)	823	28 Grade 1: 9 Grade 2: 19 Grade3: 0 Grade 4: 0 Grade 5: 0
Build-up phase reactions	302 Early: 200 Late: 102	6 Early: 4 Late: 2
Maintenance phase reactions	521 Early: 408 Late: 113	22 Early: 9 Late: 13

SCIT: Subcutaneous immunotherapy.

In order to evaluate the efficacy of the allergen-SIT treatment the symptom scores (SS), medication scores (MS), combined symptom scores (CS), and VAS scores of each patient at baseline, mid-treatment and end treatment were calculated and compared. When the SCIT patients were evaluated, there was a statistically significant ($p < 0.0001$) improvement trend in all of these scores for both asthma and ARC patients (Table III). The most significant ($p < 0.0001$) decreases were denoted for the symptom, medication, combined and VAS scores in ARC patients, and symptom, combined and VAS scores for asthma patients, when baseline and end-SCIT values were compared. Separate evaluation of SLIT patients revealed that there was a significant decrease in the ARC symptom, medication, combined and VAS scores. Asthma symptom, combined and VAS scores also showed a significant decrease in asthmatic patients ($p < 0.05$), but the asthma medication scores were not significantly different ($p > 0.05$) (Table IV).

Among the patients with asthma (± ARC) who underwent SCIT, the response to treatment was defined as high in 88.8%, low in 5.6%, and failure in 5.6%, according to combined asthma scores and high in 85.2% low in 7.4%, and failure in 7.4% according to the ARC combined scores.

Table III: The efficacy of SCIT according to scoring systems.

	Baseline Median (Q1-Q3)	2-3 years at SCIT (mid-SCIT) Median (Q1-Q3)	After completion of SCIT (end-SCIT) Median (Q1-Q3)	p value*
ARC symptom score	2.14 (1.85-2.57)	1.14 (1.14-1.85)	0.28 (0.00 -0.75)	<0.0001
ARC medication score	2.00 (2.00-2.00)	1.00 (1.00-1.00)	0.00 (0.00-0.00)	<0.001
ARC combined score	2.07 (1.92-2.42)	1.07 (1.00-1.50)	0.15 (0.00-0.57)	<0.0001
ARC VAS	420 (360-460)	210 (120-240)	40 (0.00-120)	<0.0001
Asthma symptom score	2.75 (1.43-3.00)	1.37 (0.37-2.00)	0 (0.00-0.81)	<0.0001
Asthma medication score	1.50 (1.00-2.00)	1.00 (0.00-1.00)	0.00 (0.00-1.00)	<0.0001
Asthma combined score	2.00 (1.59-2.50)	1.00 (0.37-1.75)	0.00 (0.00-0.90)	<0.001
Asthma VAS	320 (240-327)	100 (35-240)	0.00 (0.00-70.0)	<0.0001

*p value denotes the significance of change trend in median scores from baseline to mid- and end-SCIT. All scores at different time points showed a statistical significant ($p < 0.05$) decrease. The most significant ($p < 0.0001$) decreases were denoted for the following comparisons: ARC SSs at baseline-end; ARC MSs at baseline-end; ARC CSs at baseline-end; ARC VAS at baseline-end; baseline-mid, mid-end, Asthma SSs at baseline-end; Asthma MSs at baseline-end; Asthma CSs at baseline-end; Asthma VAS at baseline-end, **SCIT:** Subcutaneous immunotherapy, **ARC:** Allergic rhinoconjunctivitis, **VAS:** Visual analog score, **CS:** Combined score, **SS:** Symptom score, **MS:** Medication score.

Table IV: The efficacy of SLIT according to scoring systems.

	Baseline median (Q1-Q3)	2-3 years at SLIT (mid-SLIT) median (Q1-Q3)	After completion of SLIT (end-SLIT) median (Q1-Q3)	p value*
ARC symptom score	2.00 (1.78-2.50)	0.85 (0.63-1.71)	0.29 (0.28-0.57)	0.015
ARC medication score	2.00 (1.50-2.00)	2.00 (0.50-2.00)	0.00 (0.00-1.00)	0.037
ARC combined score	2.00 (1.64-2.25)	1.85 (1.17-3.92)	0.15 (0.15-0.78)	0.015
ARC VAS	420 (360-460)	160 (115-280)	40 (3.50-50.0)	0.007
Asthma symptom score	2.25 (2.00-2.50)	1.25 (1.00-1.50)	0.50 (0.31-0.87)	0.018
Asthma medication score	2.00 (1.25-2.00)	1.50 (1.00-2.00)	1.00 (0.00-2.00)	0.156
Asthma combined score	2.00 (1.81-2.18)	1.37 (1.06-1.68)	0.68 (0.25-1.40)	0.018
Asthma VAS	265 (225-312)	90 (45-150)	25 (6.50-52.5)	0.018

*p value denotes the significance of change trend in median scores from baseline to mid- and end-SLIT. All scores at baseline and end time points showed a statistical significant ($p < 0.05$) decrease except asthma MSs. The most significant ($p \leq 0.005$) decreases were denoted for the following comparisons: ARC SS, MS, CS, VAS at baseline-end; Asthma SS, CS, VAS at baseline-end. The comparisons between baseline and mid scores were not significant. **SLIT:** Sublinguinal immunotherapy, **ARC:** Allergic rhinoconjunctivitis, **VAS:** Visual analog score, **CS:** Combined score, **SS:** Symptom score, **MS:** Medication score.

Among the patients with asthma (± ARC) who underwent SLIT, the response to treatment was defined as high in 50% and low in 50% according to combined asthma scores, and high in 80% and low in 20% according to the ARC combined scores. The rate of asthma high responders was not significantly different from that of low responders.

Among the patients with ARC who underwent either SCIT or SLIT all of them showed a high degree of response to treatment, according to the combined ARC scores.

The clinical and laboratory parameters that result in high treatment response (a decrease above 50% in combined asthma and ARC scores) to SIT were searched for by regression analysis. For asthma (± ARC) patients gender, age at diagnosis, SPT edema diameter, total IgE, peripheral eosinophil count, spirometric values, FEV1 and MMEF reversibility, PC20 value, asthma and ARC scores, number of aeroallergen sensitivity before allergen-SIT, allergen-SIT type, SIT allergen number and content, allergen-SIT adjuvant, allergen-SIT injection number, and local and systemic side effects were included in the analysis. The results revealed that patients with higher baseline scores before allergen-SIT and who were given more injections showed a significantly increased rate of high treatment response. Multivariate logistic regression analysis could not reveal any statistically significant independent variable.

DISCUSSION

Allergen-SIT is an effective treatment method aiming for controlled administration of the sensitized allergen in increasing doses in order to develop immune and clinical tolerance (14). In the present study, the effectiveness of allergen immunotherapy, frequency of LRs and SRs and the variables affecting these parameters were investigated in all patients who underwent allergen-SIT during a 5-year period. Our results showed that SCIT was highly successful in the treatment of asthma and ARC in terms of the rate of therapeutic response. Although SLIT resulted in a high rate of good response in ARC patients, the response rate was lower in asthmatic patients. Systemic side effects were very low as a result of close risk monitoring and dose adjustments performed.

Although allergen-SIT is a quite effective treatment method in asthma and ARC, its use is limited by its local and especially systemic side effects and failure to respond in some clinical circumstances (5,6). LRs are common in 26-86% of patients receiving SCIT and are mostly well tolerated (15,16). Li et al. reported LRs in 64.8% of injections in patients who underwent mite-allergen SCIT (17). In our study, LRs were observed in 79.3% of patients and 18% of total injections. Logistic regression analysis revealed that high number of total injections increased the risk of LRs, while gender, age of diagnosis, IT allergen number and content, IT adjuvant content, and the number of injections administered in each session did not affect the incidence.

In the SCIT surveillance study conducted by the American Academy of Allergy Asthma and Immunology (AAAAI) among 9.1 million injections performed between 2008 and 2016, it was reported that 8.7 SRs, including 5.6 grade 1, 2.7 grade 2, 0.35 grade 3, and one death case, were observed in every 10.000 SCIT injections. Between 2013 and 2016, SRs occurred in 0.6% of patients who underwent SCIT, and grade 4 SRs were observed in 0.005% of patients (18). The risk of SR development varies according to the protocol used, with rates varying between 0.06-3.2% have been reported in different studies (7, 19-26). The studies performed in our country have reported that SRs occurred between 0.3 to 0.6 % of total injections during SCIT for mite, pollen and venom allergies (27, 28). In the present study, a total of 4567 injections were applied and SRs were observed in 0.6% of all injections; 32.1% were Grade1 and 67.9% were Grade 2 reactions, while anaphylaxis or fatal reaction was not observed. On the other hand,63.3% of LRs and 78.6% of SRs occurred in the maintenance phase.

In a study conducted in Turkey, 126 patients (88 grass pollen, 18 house dust mite and 20 venom allergies) who received 4705 injections of rush, cluster or conventional allergen-SIT, and who had no premedication before SCIT, were analyzed. The rate of SRs was 1.3% SR per injection, Rush (1.8%) and cluster (2.8%) programs were associated with a higher SR rate per injection compared to conventional SCIT (0.9%). 80% of the SRs were observed in the initial dose increasing phase and mostly with pollen extracts (75.5%) (25). However, in another study including 234 HDM sensitive patients with a diagnosis of asthma and ARC, SRs were reported at a higher rate (3.1% of 7679 injections), and patients younger than 14 years old and patients with asthma showed increased risk of SRs (17). Another study also revealed that most fatal systemic side effects were seen in asthma patients with poor asthma control (29). In a 30-year retrospective study reported from Italy including 2200 patients diagnosed with asthma

± ARC that received mite and/or pollen conventional SCIT, female gender, asthma, Parietaria allergen content, and administration of two vaccines in each session have been found to increase the risk of LRs and SRs (30). In the study by Nacaroglu et al. (31) from Turkey, SRs were found to be significantly higher in SCIT with multiple allergens in ARC patients accompanied by asthma, however, no statistically significant relation was found between adjuvant / allergen content and the frequency of side effects. It has also been reported that vaccines containing calcium phosphate produced less side effects (32). In our study, asthma diagnosis was not found to be a risk factor for SRs in patients undergoing SCIT. This may be explained by inclusion of mild-moderate degree asthmatic patients under good control, close monitoring of the symptoms and PEF values of the patients before and after immunotherapy, and suitable dose reduction strategies during the pollen season and symptomatic periods. On the other hand, it was found that a high total number of injections increased the risk of LRs and SRs, while the gender, number of injections applied in each session, allergen content, allergen-SIT content more allergens and adjuvant content did not affect the incidence. Since conventional SCIT was applied to all patients in our study, the risk of side effects could not be compared according to the SCIT protocols.

SLIT has an impressive safety profile in clinical trials (33, 34). Although there are case reports of severe allergic reactions, including anaphylaxis, no deaths have been reported (35, 36). Randomized controlled studies have shown that LRs with SLIT can be up to 80% in frequency. SLIT can often cause swelling in the mouth, lips and tongue, and local itching in the throat, which can continue for weeks (8, 37). More recently, several large placebo-controlled studies have demonstrated the safety of SLIT in patients with seasonal and perennial allergic rhinitis. In a large study of 1.500 children and adults treated with SLIT grass tablets for seasonal allergic rhinitis, Maloney et al. reported transient LRs defined by irritation in the throat, itching or paresthesia in the oral mucosa, edema in the mouth and ear itching in 79% of the patients treated. In this study, there were no cases of severe anaphylaxis due to treatment, but 6% of the individuals discontinued the treatment due to local side effects related to the treatment (38). In our study, complaints of local itching and swelling in the throat and palate developed in three (16.7%) of the patients who underwent SLIT (n=18) and spontaneously resolved in the follow-up of the patients, and no systemic reaction was observed in any patient.

Currently, SCIT is recommended in patients with aeroallergen-sensitive ARC and/or allergic asthma (39, 40). In a systematic review and meta-analysis including 160 studies, Dhami et al. (5) showed that SCIT reduced symptom, drug and combined scores in patients with ARC and was an effective treatment modality. The preventive allergy treatment study (PAT study) was one of the first major studies to evaluate SCIT' s preventive role. In this study, it was shown that asthma symptoms evaluated by clinical diagnosis were significantly less in children with ARC who had SCIT with standard grass and/or birch allergen extracts. According to these data, it has been shown that allergen-SIT can reduce the development of asthma in children with seasonal rhino conjunctivitis (41). In 2017, Dhami et al. (6) investigated the efficacy of SCIT in reducing asthma symptoms and drug use with a meta-analysis of 98 studies, showing a reduction in short-term symptoms and drug scores in allergic asthma. In a recently published Cochrane review evaluating 3459 asthmatic patients and 88 clinical trials, it was shown that SCIT reduced asthma symptoms (Standardised Mean Difference (SMD), -0.59; 95% CI, -0.83-0.35), medication use (SMD, -0.53; 95% CI, -0.80-0.27) and bronchial hyper reactivity (SMD, -0.35; 95% CI, -0.59-0.11). This analysis revealed that the decrease in symptom scores was more significant in mite and pollen SCIT (42). In the present study, a significant decrease was found in asthma and ARC symptom, medication, combined and VAS scores after completion of SCIT compared to baseline ($p<0.0001$) in patients with a diagnosis of asthma (± ARC) that underwent SCIT. Among these patients the response rates were high in 85.2%, low in 7.4%, and failure in 7.4%, according to the ARC combined scores, and high in 88.8%, low in 5.6%, and failure in 5.6% according to combined asthma scores.

In a prospective study by Wu et al. (43), 3-years SCIT treatment of 144 children with allergic asthma and rhinitis was analyzed. After 3 years of SCIT treatment, the FEV1 had significantly and proportionally increased with the duration of the treatment. A recent Cochrane meta-analysis assessed the effects of allergen-SIT on asthma. When lung function outcomes were analyzed, there was an overall trend for improvement in lung function, although heterogeneity was noted among studies (42).

In a study by Beigh et al. (44), a total of 80 patients with mild allergic asthma who received SLIT were recruited. There was a significant increase in the post treatment total IgE, FEV1% and FEV1/FVC values compared to baseline. Moreover, they found an insignificant decrease in the peripheral eosinophil count, in accordance with our study. In the present study, a significant improvement was found in post treatment mean MMEF% values compared to baseline, while FEV1 and FEV1/FVC was not significantly different. This result may point out that SCIT may cause significant improvement in small airway disease, reflected in MMEF values which is an early marker of asthma, then FEV1% values that are generally normal in mild asthmatic children. This result is also compatible with our findings for asthma clinical and medication scores. However, in the SLIT group a significant improvement was found only in mean PEF values, in accordance with the limited effect of SLIT on the asthmatic scores in our patients.

Studies comparing the effects of SCIT and SLIT over the years have yielded conflicting results. Nelson et al. (45), published a meta-analysis reporting the superiority of SCIT over SLIT in 2016. There is clear evidence that SLIT is significantly effective in reducing nasal and ocular symptoms, medication use, and symptom-medication score in children with ARC (1,5,39,46). SLIT efficacy in children has been shown for perennial and seasonal allergens, for pre-seasonal and continuous programs (5). In our study, when patients diagnosed with asthma ± ARC who underwent SLIT were evaluated separately, ARC symptom, medication, combined and VAS scores and asthma symptom, combined, and VAS scores at the mid- and end of treatment period showed a significant decrease when compared to the pre-treatment scores. However, no significant decrease was found for asthma medication scores. Among the asthmatic SLIT group, the response rates were high in 50% and low in 50% according to asthma combined scores and not significantly different. On the other hand, all the patients with ARC who underwent SLIT were evaluated as high responders according to the combined ARC scores. These results pointed out that SLIT was less efficient in decreasing asthma medication needs and scores, when compared to ARC scores.

In conclusion, approximately 85 to 90% of asthmatic patients on SCIT and 50% of asthmatic patients on SLIT showed a high treatment response in asthma related scores. On the other hand, all of the non-asthmatic ARC patients showed high response rates in scores with both SCIT and SLIT treatment. The incidence of systemic side effects was very low and they were mostly mild, as a result of close monitoring and dose adjustments.

REFERENCES

1. Jutel M, Agache I, Bonini S, Burks AW, Calderon M, Canonica W, et al. International consensus on allergy immunotherapy. J Allergy Clin Immunol 2015;136:556-68.
2. Noon L. Prophylactic inoculation against hay fever. Lancet 1911;177(4580):1572-3.
3. Freeman J. Further observations on the treatment of hay fever by hypodermic inoculations of pollen vaccine. Lancet 1911;178(4594):814-7.
4. 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.
5. Dhami S, Nurmatov U, Arasi S, Khan T, Asaria M, Zaman H, et al. Allergen immunotherapy for allergic rhinoconjunctivitis: A systematic review and meta-analysis. Allergy 2017;72(11):1597-631.
6. 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.
7. 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): 569-574, 574.e1-574.e7.
8. Dahl R, Kapp A, Colombo G, de Monchy JG, Rak S, Emminger W, et al. Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis. J Allergy Clin Immunol 2006;118(2):434- 40.
9. Canonica GW, Baena-Cagnani CE, Bousquet J, Bousquet PJ, Lockey RF, Malling HJ, et al. Recommendations for standardization of clinical trials with allergen specific immunotherapy for respiratory allergy. A statement of a World Allergy Organization (WAO) task force. Allergy 2007;62(3):317-24.
10. Song Y, Long J, Wang T, Xie J, Wang M, Tan G. Long-term efficacy of standardised specific subcutaneous immunotherapy in children with persistent allergic rhinitis due to multiple allergens including house dust mites. J Laryngol Otol 2018;132(3): 230-5.
11. Gao Y, Lin X, Ma J, Wei X, Wang Q, Wang M. Enhanced efficacy of dust mite sublingual immunotherapy in low-response allergic rhinitis patients after dose increment at 6 months: A prospective study. Int Arch Allergy Immunol 2020;181(4):311-9.
12. Allergen Immunotherapy: National Guideline 2016. Asthma Allergy Immunol 2016;14 (Suppl.1): S61-S63.

13. Canonica GW, Cox L, Pawancar R, Baena-Cagnani CE, Blaiss M, Bonini S, et al. Sublingual immunotherapy: World Allergy Organization position paper 2013 update .World Allergy Organ J 2014;7(1):6.
14. Pfaar O, Agache I, de Blay F, Bonini S, Chaker AM, Durham SR, et al. Perspectives in allergen immunotherapy: 2019 and beyond. Allergy 2019;74(Suppl 108):3-25.
15. Petalas K, Durham SR. Allergen immunotherapy for allergic rhinitis. Rhinology 2013;51(2):99-110.
16. Adamic K, Zidarn M, Bajrovic N, Erzen R, Kopac P, Music E. The local and systemic side-effects of venom and inhaled-allergen subcutaneous immunotherapy. Wien Klin Wochenschr 2009;121:357-60.
17. Li MR, Wang XN, Jiang HD, Wang QY, Li YC, Lin J, et al. Zhonghua Er Ke Za Zhi 2012;50(10):726-31.
18. 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.
19. Winther L, Arnved J, Malling HJ, Nolte H, Mosbech H. Side effects of allergen specific immunotherapy: A prospective multi-centre study. Clin Exp Allergy 2006; 36: 254-60.
20. Gastaminza G, Algorta J, Audicana M, Etxenagusia M, Fernandez E, Munoz D. Systemic reactions to immunotherapy: Influence of composition and manufacturer. Clin Exp Allergy 2003;33:470-4.
21. Can D, Demir E, Tanaç R, Gülen F, Yenigün A. Immediate adverse reactions to immunotherapy. J Investig Allergol Clin Immunol 2003;13(3):177-80.
22. 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;2:161-7.
23. Ross RN, Nelson HS, Finegold I. Effectiveness of specific immunotherapy in the treatment of allergic rhinitis: An analysis of randomized, prospective, single or double-blind, placebo-controlled studies. Clin Ther 2000;22:342-50.
24. Calderon MA, Alves B, Jacobson M, Hurwitz B, Sheikh A, Durham S. Allergen injection immunotherapy for seasonal allergic rhinitis. Cochrane Database Syst Rev 2007;2007(1):CD001936.
25. Dursun AB, Sin BA, Oner F, Misirligil Z. The safety of allergen immunotherapy (IT) in Turkey. J Investig Allergol Clin Immunol 2006;16(2):123-8.
26. Dong X, Huang N, Li W, Hu L, Wang X, Wang Y, et al. Systemic reactions to dust mite subcutaneous immunotherapy: A 3-year follow-up study. Allergy Asthma Immunol Res 2016;8(5):421-7.
27. Azkur D, Vezir E, Civelek E , Toyran M, Erkoçoğlu M, Kaya A, et al. The frequency of large local and systemic reactions after subcutaneous immunotherapy in children. Asthma Allergy Immunol 2013;11:37-42.
28. Ediger D, Yılmaz D, Coskun F, Gozu O. Is the subcutaneous allergen immunotherapy safe enough as a treatment modality? Asthma Allergy Immunol 2010;8:150-6.
29. Lockey RF, Nicoara-Kasti GL, Theodoropoulos DS, Bukantz SC. Systemic reactions and fatalities associated with allergen immunotherapy. Ann Allergy Asthma Immunol 2001;87:47-55.
30. Di Bona D, Magistà S, Masciopinto L, Lovecchio A, Loiodice R, Bilancia M, et al; AIT Study Group. Safety and treatment compliance of subcutaneous immunotherapy: A 30-year retrospective study. Respir Med 2020;161:105843.
31. Nacaroglu HT, Erdem SB, Sumer O, Karaman S, Unsal Karkıner CS, Asilsoy S, et al. Local and systemic reactions to subcutaneous allergen immunotherapy: Ten years' experience in a pediatric clinic. Ann Allergy Asthma Immunol 2016;116(4):349-53.
32. Nelson B, Dupont LA, Reid MJ. Prospective survey of local and systemic reactions to immunotherapy with pollen extracts. Ann Allergy 1986;56(4):331-4.
33. Durham SR, Emminger W, Kapp A, de Monchy JG, Rak S, Scadding GK, et al. SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial. J Allergy Clin Immunol 2012;129(3):717-725.e5.
34. Didier A, Worm M, Horak F, Sussman G, de Beaumont O, Le Gall M, et al. Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. J Allergy Clin Immunol 2011;128(3):559-66.
35. Calderón 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.
36. Lin SY, Azar A, Suarez-Cuervo C, Diette GB, Brigham E, Rice J, et al. Role of sublingual immunotherapy in the treatment of asthma: An updated systematic review. Int Forum Allergy Rhinol 2018;8(9):982-92.
37. Virchow JC, Backer V, Kuna P, Prieto L, Nolte H, Villesen HH, Ljørring C, Riis B, de Blay F. 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.
38. Maloney J, Bernstein DI, Nelson H, Creticos P, Hébert J, Noonan M, et al. Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: A large randomized controlled trial.Ann Allergy Asthma Immunol 2014;112:146-53.e2.
39. 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.
40. Ciprandi G, Fenoglio D, Cirillo I, Tosca MA, La Rosa M, Licari A, et al. Sublingual immunotherapy: An update on immunologic and functional effects. Allergy Asthma Proc 2007;28(1):40-3.

41. Möller C, Dreborg S, Ferdousi HA, Halken S, Høst A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109(2):251-6.
42. Abramson MJ, Puy RM, Weiner JM. Injection allergen immunotherapy for asthma. Cochrane Database Syst Rev 2010 (8):CD001186.
43. Wu SJ, Chen S, Chen B, Wang L, Zeng X. An analysis of the subcutaneous immunotherapy on the pulmonary function and symptoms of asthma and rhinitis in children. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi 2017;31(17):1352-5.
44. Beigh AH, Rasool R, Kawoosa F, Manzoor S, Rashid R, Andrabi KI, et al. Improved pulmonary function test (PFT) after 1 one year of Sublingual Immunotherapy (SLIT) in unison with pharmacotherapy in mild allergic asthmatics. Immunol Lett 2021;230:36-41.
45. Nelson HS, Makatsori M, Calderon MA. Subcutaneous immunotherapy and sublingual immunotherapy: Comparative efficacy, current and potential indications, and warnings--United States Versus Europe. Immunol Allergy Clin North Am 2016;36(1):13-24.
46. Okamoto Y, Fujieda S, Okano M, Hida H, Kakudo S, Masuyama K. Efficacy of house dust mite sublingual tablet in the treatment of allergic rhinoconjunctivitis: A randomized trial in a pediatric population. Pediatr Allergy Immunol 2019;30(1):66-73.