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Maintained disease control and steroid-sparing effect of subcutaneous immunotherapy in allergic rhinitis and asthma

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Abstract

Background: Allergen immunotherapy is the only currently available treatment strategy that modifies the immune response to the causative allergen and induces clinical improvement and a steroid-sparing effect.

Objective: In this real-life study, we aimed to evaluate and compare the efficacy of subcutaneous immunotherapy (SCIT) with one allergen or multiple allergens in children and adults with asthma and/or allergic rhinitis in terms of disease control and a steroid-sparing effect.

Methods: Demographics, the initial inhaled corticosteroid (ICS) and/or intranasal corticosteroid (INS) dose, and other drugs of patients receiving SCIT for at least 12 months were recorded. Data on the final dose/use of ICS/INS and asthma and/or allergic rhinitis control were gathered.

Results: Of 104 patients included, 57.1% and 64.5% of patients with asthma and allergic rhinitis, respectively, were able to discontinue ICS and INS after SCIT. The median time to INS and ICS dose reduction was 6 months. SCIT with one allergen or multiple allergens effectively reduced the ICS and INS dose and led to control of asthma and allergic rhinitis, with no significant difference between the groups. When the efficacy of SCIT was compared in children and adults, there was no significant difference in terms of a steroid-sparing effect or the control of asthma and allergic rhinitis. SCIT was effective in both children and adult patients.

Conclusion: In this real-life observational study, we have demonstrated a marked steroid-sparing effect while maintaining control of asthma and allergic rhinitis in children and adults treated with one allergen or multiple allergens.

Key words: Allergen immunotherapy, asthma, allergic rhinitis, efficacy, inhaled steroid, intranasal steroid, steroid sparing.

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Introduction

The administration of allergen immunotherapy (AIT) by means of subcutaneous (SC) injection, which was first introduced a century ago, is effective in the management of respiratory allergic diseases and venom allergies. AIT is the only currently available treatment strategy that modifies the immune response to the causative allergen and induces clinical improvement1 and a steroid-sparing effect.[2]

According to guidelines, the concept of disease control has been proposed as the main goal of the treatment of asthma and allergic rhinitis.[3,4] Control of clinical and functional features of the disease is based on the adjustment in the regular controller treatments, inhaled corticosteroids (ICS) and intranasal corticosteroids (INS), which are accepted as the first choice of anti-inflammatory medications in both asthma and allergic rhinitis.[5,7] The dose of ICS and INS is adjusted based on disease fluctuations, but discontinuation is rarely possible. Meanwhile, in the last decade, subcutaneous immunotherapy (SCIT) has been proven to reduce asthma symptoms

and medication use, besides achieving improvement in bronchial hyperreactivity. SCIT has been proposed as an additional option in the treatment of asthma and allergic rhinitis.[3,4] Very few studies have evaluated the efficacy of SCIT regarding disease control and the reduction or discontinuation of ICS and INS.[2,8-11]

Most of the randomized controlled trials demonstrating the clinical efficacy of AIT have been conducted with single allergen extracts. In real life, however, the majority of the patients with respiratory allergies are polysensitized. Indeed, in a previous study researchers had demonstrated that the majority of the cases diagnosed with asthma and allergic rhinitis were polysensitized.[12] If only the monosensitized patients are accepted as candidates for AIT, most of the patients would not have the chance to receive disease-modifying and curative therapy.[13] Despite the high prevalence of polysensitization, evidence is scarce regarding the efficacy of AIT in polysensitized patients with asthma and/or allergic rhinitis. Thus, in this real-life study we aimed to evaluate and compare the efficacy of SCIT with one or multiple allergens in children and adults with asthma and/or allergic rhinitis in terms of disease control and a steroid-sparing effect.

Materials and Methods

Study design

This study included all patients with allergic rhinitis and/or asthma in whom allergen-specific SCIT was used for at least 12 months from May 2014 to December 2019 under follow-up in the Division of Allergy and Immunology of the Near East University Hospital. Data on age, gender, the duration of symptoms, diagnosis, the number and type of allergens sensitized, the severity of disease, the previously used medication(s), and the mean daily dose of ICS and INS at initiation of AIT were recorded retrospectively from the hospital database system. Then, data on disease control and the final dose of ICS and INS were gathered. Patients with maintained allergic rhinitis and/or asthma control with no need of ICS and INS as a controller medication for at least 6 months were defined as "steroid avoidance" patients. Since 2010, the Division of Allergy and Immunology of the Near East University Hospital has applied a standardized ICS and INS protocol. According to this protocol, in the treatment of allergic asthma and allergic rhinitis, fluticasone propionate is chosen as the only ICS and INS for standardization. Ethical approval was obtained from the Near East University Ethics committee (reference number YDU/2020/86-1249).

Asthma and allergic rhinitis diagnosis and follow-up

The diagnosis and severity of allergic rhinitis was based on the Allergic Rhinitis and its Impact on Asthma (ARIA) criteria. The diagnosis and severity of allergic asthma was based on medical history, physical examination findings, and pre-post bronchodilator changes in the forced expiratory volume in 1 s (FEV1), as described in the Global Initiative for Asthma (GINA) report. AIT is offered in patients with ongoing disease fluctuations under ICS treatment and environmental precautions.

SCIT

All patients underwent SCIT with Novo-Helisen Depot® and Allergovit Allergopharma, Reinbek, Germany) or Alutard (ALK-Abelló, Hørsholm, Denmark). SCIT was divided into two phases: an initial build-up phase and a maintenance phase. For conventional SCIT, patients received subcutaneous injections of gradually increasing doses of allergen extract every week as recommended, followed by once-a-month maintenance doses.

SCIT was applied to all patients according to the immunotherapy scheme recommended by the manufacturer. The effective maintenance doses of allergens used in the SCIT protocol were; for Novo Helisen Depot, 5000 TU/mL; for Alutard, 100000 U-SQ/mL; for Allergovit, 10000 TU/mL. Patients received either SCIT with one allergen (monotherapy), a mixture of homogenous allergens (mixed), or separate parallel injections of non-homogenous allergens (simultaneous). Those groups were compared according to ICS and INS dose reduction or discontinuation and asthma and/or allergic rhinitis control.

Skin-prick tests

A skin-prick test was performed annually with locally common aeroallergens including *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, *Alternaria alternata*, *Aspergillus* mix, *Cladosporium* mix, *Penicillium* mix, a mixture of four cereals, a mixture of 12 grasses, *Phleum pratense*, Compositae, *Urtica dioica*, *Parietaria officinalis*, tree mix, cypress, *Acacia dealbata*, *Olea europaea*, *Pinus sylvestris*, cat hair, and dog hair (Allergopharma). Histamine and dihydrochloride saline were used as positive and negative controls, respectively. A drop of each allergen extract was introduced via special lancets into the skin on the volar side of the left forearm. After 15 min, the wheal reaction was measured as the mean of the longest diameter and the length of the perpendicular line through its middle. A wheal size of at least 3 mm was considered positive.

Evaluation of clinical outcomes

Clinical responses to SCIT were categorized as follows: (a) a steroid-sparing effect and (b) control of asthma and/or allergic rhinitis.

For patients with allergic rhinitis, a steroid-sparing effect was defined as a patient who had not used INS in the last 6 months or who had used it only a few times in a year or who had used it only a few times in the last 3 months. For patients with asthma, a steroid-sparing effect was defined as a patient who had not used ICS within the last 6 months or who had used it only intermittently or who had used it less than twice in a month.

A state of controlled asthma and/or allergic rhinitis was defined as patients whose symptoms were well controlled without requiring any further rescue medication for the last 6 months of SCIT for patients with indoor allergens and at least one season for patients with seasonal allergens. An uncontrolled asthma state (according to GINA) was defined as patients with poorly controlled nightly and/or daily symptoms

with maintenance treatment requiring frequent use of rescue medicine. An uncontrolled allergic rhinitis state (according to ARIA) was defined as patients who have rhinitis symptoms under maintenance treatment.

Statistical analysis

Statistical analyses were carried out by using SPSS Statistics (Release 23.0; IBM Corp., Armonk, NY, USA). Differences between groups were tested for significance with chi-squared and t-tests. Paired t-tests were performed for between-group comparisons. A p-value < 0.05 was considered to be significant.

Results

In total, 104 patients (50 children and 54 adults) were enrolled. The demographic and clinical characteristics of these patients are shown in **Table 1**. Ten patients (9.6%) had allergic asthma, 42 patients (40.4%) had allergic rhinitis, and 52 patients (50%) had both. All patients had used SCIT for at least 12 months. Most of the patients were allergic to house dust mites and/or pollens. Most of the patients received monoallergen SCIT (54.8%), while 35.6% had simultaneous (Parallel 2) SCIT, and only 9.6% had a mixture of allergens.

Compared with the initiation of SCIT, the need for INS, antihistamines, and montelukast for allergic rhinitis, as well as the need for ICS, montelukast, and LABA for allergic asthma, declined in patients after SCIT. The detailed medical treatment of patients before and after SCIT is presented in **Figure 1**.

Steroid-sparing effect

Evaluation of the entire group based on an ICS- and INS-sparing effect of SCIT demonstrated that 57.1% of patients with asthma and 64.5% of patients with allergic rhinitis were able to discontinue ICS and INS after SCIT. Only a minority of patients had to use the same doses of ICS and INS. The distribution of ICS and INS usage after SCIT is presented in **Table 2**.

The time to INS and ICS dose reduction after SCIT

In the current study, the success of SCIT was evaluated based on a steroid-sparing effect and control of asthma and/or allergic rhinitis. The mean dose of daily ICS and INS use decreased significantly with SCIT (p = 0.0001 for both, **Table 3**). The median (range) time to ICS and INS dose reduction or discontinuation after SCIT initiation was 6 (1–24) months and 6 (1–39) months, respectively. Both monoallergen and multiple allergen immunotherapy significantly reduced the ICS and INS dose (p = 0.0001 for both, **Table 3**).

Disease control

Comparison of an ICS- and INS-sparing effect, asthma and rhinitis control of monoallergen, simultaneous, and multiple allergen SCIT is given in **Table 4**. Each modality effectively reduced the ICS and INS doses and also led to asthma and/or allergic rhinitis control. In addition, the efficacy of the three SCIT modes did not differ significantly from each other. Despite ICS/INS reduction or discontinuation,

Table 1. Baseline characteristics of patients

Parameters	
Age, mean ± SD (range)	20.49 ± 12.69 (6–55 years)
Sex, female/total (n)	49/104
Children/adult, n	50/54
Disease duration, mean ± SD (months)	78.73 ± 68.55
SCIT duration, mean ± SD (month)	25.10 ± 13.13
Disease, n (/%)	
AA only	10 (9.6%)
AR only	42 (40.4%)
AA with AR	52 (50%)
Sensitized allergen, n (%)	
House dust mites	33 (31.7%)
Pollen(s)	21 (20.2%)
HDM + pollen	27 (26%)
Alternaria	5 (4.8%)
HDM + *Alternaria*	7 (6.7%)
Alternaria + pollen	6 (5.8%)
HDM + pollen + molds	5 (4.8%)
Targeting allergen, n (%)	
HDM	42 (40.4%)
Pollen/s	24 (23.07%)
HDM + pollen(s)	20 (19.23%)
Alternaria	9 (8.7%)
HDM + *Alternaria*	5 (4.8%)
Pollen(s) + *Alternaria*	4 (3.9%)
Mode of immunotherapy, n (%)	
Monoallergen	57 (54.8%)
Simultaneous	37(35.6%)
Mix	10 (9.6%)
Severity of asthma, n (%)	
Mild intermittent	12 (18.5%)
Mild persistent	33 (50.8%)
Moderate persistent	20 (30.8%)
Severity of allergic rhinitis, n (%)	
Mild intermittent	7 (7.4%)
Moderate/severe intermittent	13 (13.7%)
Mild persistent	16 (16.8%)
Moderate/severe persistent	59 (62.1%)

Pollens: grasses, wild grasses, tree pollens
Molds: *Alternaria*, *Aspergillus*, *Penicillium*, *Cladosporium*

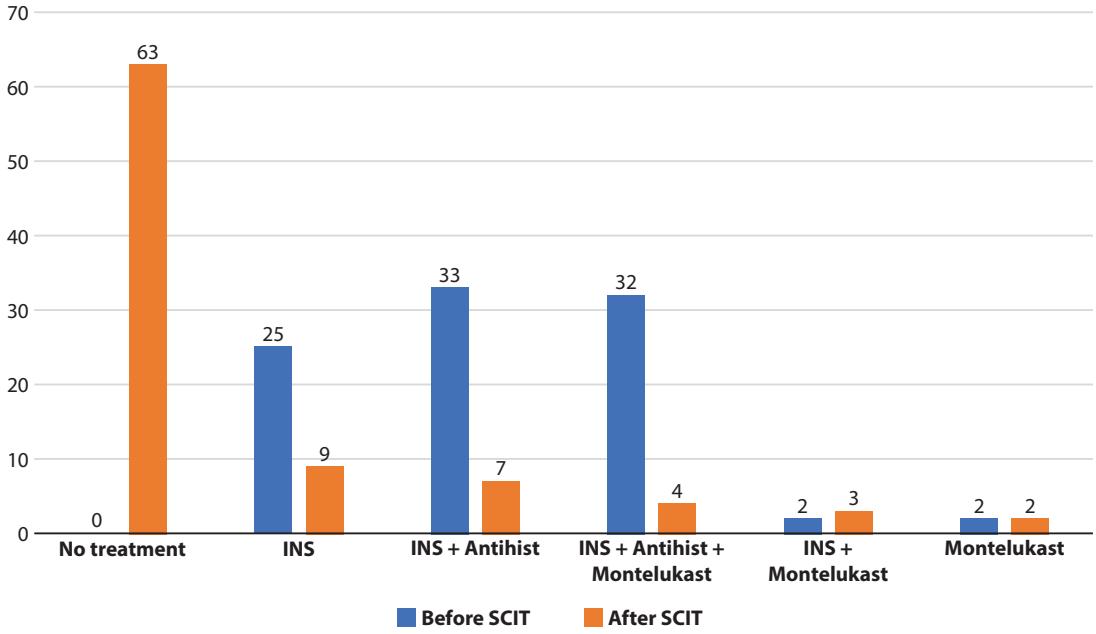

Figure 1a. Distribution of all rhinitis medications before and after SCIT
All patients with allergic rhinitis and/or asthma in whom allergen-specific SCIT was used for at least 12 months under follow-up were included in the study. The mean duration of SCIT use was 25.10 ± 13.13 months.

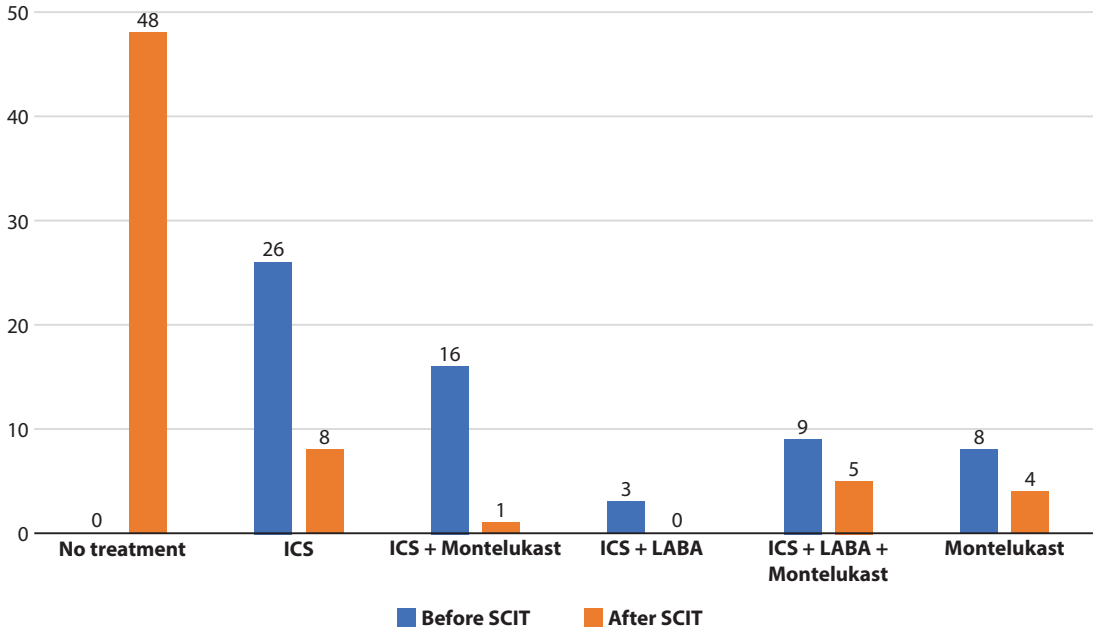

Figure 1b. Distribution of all asthma medications before and after SCIT
All patients with allergic rhinitis and/or asthma in whom allergen-specific SCIT was used for at least 12 months under follow-up were included in the study. The mean duration of SCIT interval was 25.10 ± 13.13 months.

Table 2. Distribution of ICS and INS usage after SCIT

ICS dose (after immunotherapy)	n (%)
Stop	32 (57.1%)
Intermittent usage (≤ 2/month)	8 (14.3%)
Reduced dose	13 (23.2%)
No difference	2 (3.6%)
Increased dose	1 (1.8%)
INS dose (after immunotherapy)	**n (%)**
Stop	60 (64.5%)
Intermittent usage (≤ 2/month)	17 (18.3%)
Reduced dose	9 (9.7%)
No difference	7 (7.5%)

Table 3. The success of SCIT regarding reducing the dose of ICS and INS

	Baseline, mean ± SD	Final, mean ± SD	*p*
Mono IT			
ICS dose	481.67 ± 130.65	55.83 ± 96.49	0.0001
INS dose	131.52 ± 50.50	20.50 ± 51.44	0.0001
Multiple IT			
ICS dose	459.0 ± 227.20	67.5 ± 159.17	0.0001
INS dose	176.08 ± 69.90	30.86 ± 69.97	0.0001
Entire group			
ICS dose	473.57 ± 169.75	60 ± 121.28	0.0001
INS dose	153.33 ± 64.49	25.40 ± 61.02	0.0001

Table 4. Comparison of monoallergen versus simultaneous versus multiple immunotherapy response

	Monoallergen n (%)	Simultaneous n (%)	Multiple n (%)	*P*
Steroid-sparing effect in asthma	34/36 (94.4%)	17/18 (94.4%)	2/2 (100%)	0.94
Steroid-sparing effect in allergic rhinitis	40/66 (60.6%)	34/37 (91.9%)	8/10 (80%)	0.31
Asthma control	35/39 (89.7%)	23/23 (100%)	3/3 (100%)	0.24
Rhinitis control	47/48 (97.9%)	36/37 (97.3%)	9/10 (90%)	0.42

the majority of patients had well-controlled rhinitis and asthma (**Table 4**). The compliance to SCIT in our study population was very high: 97 patients (93.27%) are still on SCIT, 3 finished after 5 years (2.88%), and only 4 patients (3.85%) discontinued treatment because of side effects.

Comparison of children and adults

When comparing the efficacy of SCIT between children and adults, there was not a significant difference in terms of ICS dose reduction (p = 0.54) and INS dose reduction (p = 0.28) or in the control of asthma (p = 0.26) and allergic rhinitis (p = 0.49). SCIT was effective both in children and adult patients.

Discussion

In this real-life study, the primary aim was to demonstrate the equivalent efficacy of SCIT with one and multiple allergens in patients with allergic rhinitis and/or asthma. Disease control and retained discontinuation of ICS and INS were the primary endpoints. When considering the entire study group, there was a significant reduction in the mean daily dose of ICS and INS, but more importantly, there was a steroid-sparing effect—retained discontinuation or intermittent use—of 57.1% or 14.3%, respectively, for ICS and 64.5% or 18.3%, respectively, for INS. The median time to this decrease or discontinuation of ICS and INS dose after initiation of SCIT was 6 months. In addition, the use of all the other medications decreased (**Figure 1**).

Comparison of patients receiving SCIT with one or multiple (parallel or mixed) allergens in terms of a steroid-sparing effect and asthma and/or rhinitis control revealed no significant differences between groups. Comparison of pediatric or adult patients in terms of a steroid-sparing effect and control of asthma and/or allergic rhinitis also revealed no significant differences. The results of this real-life observational study demonstrate that the efficacy of SCIT with multiple allergens in polysensitized patients is equivalent to SCIT with one allergen in monosensitized patients. In addition, the efficacy in children is comparable to that in adults.

Although there are a number of sublingual immunotherapy (SLIT) studies comparing the efficacy of AIT with multiple allergens,[14,15] there is a dearth of studies evaluating the efficacy of SCIT with multiple allergens. While SCIT with two parallel allergens is widely used in clinical practice, there has been comparison of its efficacy with monoallergen SCIT in monosensitized patients. Therefore, the results of this study contribute to the current SCIT applications of allergy practitioners.

In a pilot SLIT study, 16 subjects sensitized to ≥ 6 allergens were randomized to receive SLIT with one, three, or all sensitized allergens. The rhinitis combined symptom score (SS) and quality of life (QoL) improved significantly in all groups, with no significant differences between the three study groups. On the other hand, none of the groups showed a decrease in the number of daily medications used.[14]

In that study, all patients were polysensitized; the vials for patients who received three or all sensitized allergens contained of mixtures of all allergens, regardless of homogenous allergen group principles. In other words, indoor and outdoor allergens were mixed in the same vial. The absence of a decrease in the number of daily medications used may be due to this fact. In our study, all the allergen preparations were based on homogenous allergen group principles, with mixtures only within homogenous groups; otherwise, they were administered in separate vials.

In another open-label, controlled SLIT study conducted by Marogna et al.,[15] allergic patients with rhinitis and asthma sensitized to both birch and grass were randomized to receive SLIT with only birch or grass, SLIT with both birch and grass (but administered separately), or pharmacotherapy for 4 years. Although the pharmacotherapy group did not improve in the evaluated parameters, the three SLIT groups revealed significant clinical improvement and a reduction in the nasal eosinophil number. The participants receiving both allergens improved significantly more than the other two SLIT groups. The authors concluded that SLIT with two separate allergens provided the best results.[15]

One of the most important parameters we assessed is a steroid-sparing effect of SCIT in asthma and allergic rhinitis. In one study, 54 adults with asthma sensitized to house dust mites (HDM) receiving a daily ICS doses equivalent to 500 µg fluticasone propionate were randomized to receive SCIT with HDM or placebo for 3 years. ICS doses were assessed at baseline and yearly. The decline in the daily ICS dose was 82% after 2 years in patients with moderate-to-severe asthma, and 90% in patients with moderate asthma. That study demonstrated a steroid-sparing effect of SCIT with HDM in monosensitized adults with moderate-to-severe asthma.[8] There was a significant decline in the daily ICS and INS doses in our study in participants who received SCIT with one allergen or multiple allergens. In addition, the majority of our patients were able to discontinue daily INS (82.8%) and ICS (71.4%) after 6 months. This high percentage of retained discontinuation may be due to the fact that the majority of our patients with asthma had a mild, persistent form of the disease. Initiation of AIT in milder forms of asthma seems to increase the chance of retained discontinuation of ICS.

Although SCIT studies on the steroid-sparing effect are scarce, a number of studies have shown a steroid-sparing effect of SLIT. Ozdemir et al.[10] demonstrated a steroid-sparing effect of HDM SLIT in monosensitized children with asthma. Children were randomized to receive either SLIT or only pharmacotherapy and were evaluated annually for 3 years. The mean daily ICS dose decreased significantly only in the SLIT group. In addition, 53% of children in the SLIT group were able to discontinue ICS treatment, but only 9.1% in the pharmacotherapy group could discontinue ICS.[10]

In another recent study, Mosbech et al.[16] evaluated persistent mild-to-moderate asthma in patients > 14 years old in a double-blind placebo-controlled (DBPC) manner; patients received SLIT with HDM or placebo. The ICS dose was standardized at baseline and adjusted throughout the study to the lowest dose providing asthma control. At the end of the first year, those receiving SLIT with 6 SQ HDM showed a significant reduction in daily ICS dose compared with patients receiving placebo. The relative mean and median reduction was 42% and 50%, respectively, for the 6 SQ HDM group, and 15% and 25%, respectively, for the placebo group. The study demonstrated that a SLIT tablet with HDM has a certain steroid-sparing effect and therefore provides a noticeable benefit for asthma control in patients with HDM-induced persistent mild-to-moderate asthma.[16]

In another DBPC study conducted by de Blay et al.,[17] 607 patients with HDM-induced asthma were studied. After randomization, the budesonide dose was decreased with 3–4-week intervals until the Asthma Control Questionnaire (ACQ) score revealed loss of control. Then, the dose was increased until regain of asthma control. At the end of 1 year, the reduction in ICS use and dose was assessed. The mean daily ICS dose decreased significantly, and 59% of those receiving SLIT with HDM were able to decrease or quit ICS, whereas only 4% of the placebo group could stop ICS treatment.[17]

In another observational SLIT study, 70% of children with asthma being treated with SLIT with either one allergen or multiple allergens (homogenous mixture or separate) were able to discontinue ICS. In that study, retained ICS avoidance rates were not statistically different in the comparison of monosensitized versus polysensitized children receiving SLIT with one or multiple allergens.[2]

Taken together, the above-mentioned studies confirm a steroid-sparing effect of both SCIT and SLIT in patients with asthma and/or allergic rhinitis. In addition, our study provides new data on a steroid-sparing effect of SCIT with one allergen or multiple allergens (either two allergens simultaneously or homogenous mixtures) detectable as early as 6 months after the start of treatment in both children and adults.

In conclusion, in this real-life observational study we have demonstrated a marked steroid-sparing effect while maintaining control of asthma and/or allergic rhinitis in children and adults treated with one allergen or multiple allergens. Long-term studies are needed to observe whether control of asthma and/or rhinitis without use of regular steroid could be maintained.

Acknowledgment

None

Conflict of interest

None

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