Allergic Rhinitis and its Impact on Asthma scores in asthmatic patients with and without allergic rhinitis

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Background
Allergic rhinitis and allergic asthma are chronic inflammatory conditions that frequently coexist, both with hallmark eosinophilia. Immunotherapy is an established treatment for allergic diseases. Noninjective routes for immunotherapy, such as the sublingual route, are thought to be valuable therapeutic options for respiratory allergy.

Aim of the study
In the present study, sublingual immunotherapy (SLIT) using multiple allergens was administered to allergic asthmatic patients with and without allergic rhinitis aiming to evaluate the clinical efficacy of and changes in allergen-specific antibodies during SLIT and its effect on control of asthma severity and nasal allergy scores.

Patients and methods
The study included 40 patients in two groups: group I included 20 asthmatic patients and group II included 20 patients with both proven bronchial asthma and allergic rhinitis. All patients were subjected to assessment of the status of asthma and hence its degree of control using the Global Initiative for Asthma (GINA) guidelines; patients received SLIT according to the results over a period of 1 year and were clinically reassessed monthly. In addition, for the recruited candidates, the initial total immunoglobulin E (IgE) levels were measured and pulmonary function tests were performed at the time of recruitment and repeated after 6 months and 1 year of the initiation of the course of SLIT. SLIT was stopped for asthmatic patients during acute exacerbation and resumed after complete asthma control.

Results
There was a statistically significant decrease in blood eosinophils but a statistically insignificant decrease in total IgE 1 year after SLIT in both groups. Results of specific IgE to food and inhalants revealed that there was statistically significant reduction in the number of allergens in both groups 1 year after SLIT. Results of the skin prick test revealed similar results. Our results revealed that the scores of, both Allergic Rhinitis and its Impact on Asthma and GINA had improved in all patients after 1 year of continuous therapy.

Conclusion
SLIT is a safe treatment strategy that significantly reduces symptoms and medication requirements and improves asthma control in both asthmatic patients with and without allergic rhinitis. SLIT using multiple allergens lowered the allergen burden in both asthmatic patients with and those without allergic rhinitis.

Level of evidence
1b (Clinical Decision Rule tested within one clinical center).

Keywords:
allergic rhinitis, bronchial asthma, multiple allergens, sublingual immunotherapy

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Introduction

Asthma is a chronic inflammatory pulmonary disorder that is characterized by reversible obstruction of the airways [1]. The characteristics of asthma are airway inflammation and peripheral airway spasm, resulting in cough, wheezing, shortness of breath, and physical activity limitations. The goal of asthma treatment is to achieve symptom control for prolonged periods, prevent asthma exacerbations, control airway inflammation, and maintain pulmonary function. The most recent Global Initiative for Asthma (GINA) classification is based on the level of asthma control, using clinical symptoms and lung function to define whether the patient's asthma is controlled, partly controlled, or uncontrolled [2].

In addition, allergic rhinitis is a common condition that, at its most severe, can significantly impair the quality of life, despite optimal treatment with antihistamines and topical nasal corticosteroids [3].

Allergic rhinitis and allergic asthma are chronic inflammatory conditions that frequently coexist, both with hallmark eosinophilia. Rhinitis or rhinosinusitis usually occurs in more than 75% of patients with allergic asthma [4]. It is postulated that rhinitis and

asthma represent the manifestations of one syndrome in two parts of the respiratory tract, the upper and lower airways, respectively. At the low end of the severity spectrum, rhinitis may occur alone, and at the high end rhinitis and asthma may both be present, with the severity of each condition tracking in parallel. Disease manifestations in the upper and lower airways may be linked through a systemic inflammatory response [5].

According to Allergic Rhinitis and its Impact on Asthma (ARIA) [6], allergen-specific immunotherapy is indicated in patients with moderate–severe intermittent or persistent allergic rhinitis and rhinoconjunctivitis, particularly in those who do not respond sufficiently to current pharmacological treatment [7].

Immunotherapy is an established treatment for allergic diseases. Subcutaneous allergen immunotherapy is clearly beneficial in the treatment of select patients with allergic rhinitis or asthma. However, this therapy is underused, partly because it requires administration in a medical facility [8]. Noninjective routes for immunotherapy, such as the sublingual route, are thought to be valuable therapeutic options for respiratory allergy and have the primary aim of minimizing the risk of adverse events and of improving the compliance of patients [9]. Sublingual immunotherapy (SLIT) is gaining widespread attention as a viable alternative to subcutaneous immunotherapy for the treatment of allergic rhinoconjunctivitis. In addition, SLIT has been studied in other allergic disorders, including asthma [10]. SLIT is a form of allergen immunotherapy that involves administration of the allergen under the tongue. It appears to be associated with fewer serious adverse effects than subcutaneous immunotherapy, which allows home administration [8]. The mechanism of action of both injection and SLIT remains under investigation, and injection immunotherapy has been proven to lead to long-term changes in the immunologic response to allergen that may persist for years following discontinuation [11].

Aim of the study

The purpose of this study was to evaluate the clinical efficacy and safety of and changes in allergen-specific antibodies during SLIT in asthmatic patients with and without allergic rhinitis, with subsequent improvement in the asthma and allergic rhinitis scores (GINA and ARIA scores).

Patients and methods

This study was conducted at Ain-Shams University Hospitals over a 3-year period from October 2009 to October 2012 and comprised two groups: group I included 20 asthmatic patients and group II included 20 asthmatic patients with allergic rhinitis recruited in a 2-year follow-up study. The administration of specific SLIT was planned to last for at least 12 months from the commencement of therapy.

All recruited patients who agreed to be included in the study were subjected to the following investigations before commencement of any intervention:

(1) Careful history taking, clinical examination, and laboratory investigation to exclude any systemic condition that would contraindicate the modality of treatment or alter the results or their interpretation, such as diabetes or any immunologic disorder besides allergy.
(2) Chest radiograph to exclude any associated chest comorbidity.
(3) Laboratory investigation that included the following:
    (a) Routine complete blood count including the eosinophilic blood count.
    (b) Random blood sugar level.
    (c) Renal and liver functions tests.
    (d) Determination of total immunoglobulin E (IgE) in serum by means of the ELISA technique before start and after 6 months and 1 year of the course of the SLIT, using a kit supplied by Bender Med Systems diagnostics (Bender Med systems Diagnostics, Vienna, Austria).
    (e) Determination of specific IgE to food and inhalants in serum by means of RAST before start and after 6 months and 1 year of the course of the SLIT, using the Allergy Screen Panel 2, Immunoblot R-Biopharm AG, Darmstadt, Germany for analyzing specific IgE in human serum. The commercially available RIDA Allergy Screen test was used as an in-vitro diagnostic for the semiquantitative determination of circulating allergen-specific IgE in human serum. The acquired test is based on the principle of the immunoblot assay. Special allergens are bound to the surface of nitrocellulose membranes lying in a reaction trough. The patient's serum is pipetted into the reaction trough and incubated at room temperature. During this time, the allergen-specific IgE antibodies react with the allergens and bind to the nitrocellulose membranes through the allergen. Nonbound material is removed by washing. After this, an anti-human IgE antibody coupled with biotin is added and incubated at room temperature. This binds to the respective specific IgE

in the test fields from the first incubation. Nonbound detector antibodies are removed by washing. Next, streptavidin is added, which is conjugated with alkaline phosphatase and incubated at room temperature. This binds to the biotin from the second incubation in the test fields and to the positive control. Nonbound streptavidin conjugate is removed by washing. After adding the substrate and incubating at room temperature, a specific enzymatic color reaction of the alkaline phosphatase takes place, which results in the formation of precipitates on the test strips. The coloration is directly proportional to the specific antibody content of the serum sample. Evaluation is carried out after complete drying of the test strip in the RIDA X-screen, R-Biopharm AG, Darmstadt, Germany or with a loss of accuracy using the relevant evaluation template provided with the test kit. A semiquantitative determination of specific IgE antibodies against a panel of individual allergens in human serum was performed using the color template, comparing the color bands on the strip with those on the color template using the RIDA X-screen.

(4) Routine endoscopic nasal examination to verify or exclude signs of allergic rhinitis.
(5) Skin prick test directed at a battery of selected environmental allergens; reaction to 56 allergens was tested before start and after 1 year of the course of the SLIT. Patients had to stop steroids and antihistamines 48 h before the test. Interpretation of results: Prick tests measured the wheal diameter of allergens (positive test: $D/2$ = 3 mm). The reaction was read by comparing the erythema (redness) and/or induration with that of negative and positive controls: negative = no reaction or less than that of negative control; 1 + = reaction more than that of negative control and less than half that of positive control; 2 + = reaction more than half that of positive control; 3 + = reaction equal to that of positive control; and 4 + = reaction more than that of positive control. The positive control used was histamine or codeine phosphate and the negative control was phenolated/phenolated glycerol saline.
(6) Assessment of the status of asthma and hence its degree of control using the GINA guidelines, classifying them into 'controlled', 'partly controlled', and 'uncontrolled' groups.
(7) In addition, patients in group II underwent a CT scan of the paranasal sinuses to assess the status of the sinuses, and their stage of allergic rhinitis was documented using the modified ARIA score system [12].

Accepted patients received SLIT according to the results over a period of 1 year and were clinically reassessed monthly for a period of at least 1 year. In addition, the total IgE levels and clinical scores were remeasured after 6 months and 1 year of the initiation of the course of SLIT.

The choice of the allergen to be employed for SLIT was made in accordance with the combination of clinical history and results of the skin prick tests. Polysensitization, that is, the occurrence of multiple positive responses, did not exclude SLIT, which may be performed with the clinically most important allergens [9]. All significantly positive antigens (endpoint>3) were included in each patient's SLIT treatment regimen. Sublingual specific immunotherapy should be given at least for 12 months. No former specific immunotherapy was documented in any of the studied patients. Maintenance dosage was reached after 6 months.

Proportions of the various allergens used were specified on each immunotherapy set. Thus, each treatment was individually formulated. The extract suspended in extracting fluid (Coca's solution) containing 50% glycerine intraperitoneally was standardized according to the w/v ratio of native material to the extracting fluid. Each course was provided as a multidose vial of allergens, with color code in graded strengths as follows: strength 1, black label, 0.01% w/v; strength 2, green label, 0.1% w/v; strength 3, blue label, 1% w/v; and red label, maintenance set, 1% w/v.

The maintenance dose (strength 3) was recommended to be continued for 3 years. Dosage patterns were devised according to patients' sensitivity and tolerance. Care was taken to increase the dose at regular intervals; however, it could be increased only if the previous dose had been tolerated without any reaction. In case there was a gap in treatment for more than 2 weeks, therapy was reinitiated (for safety reasons) with half of the previously given dose. In the event of interruption for more than 4 weeks, the therapy was resumed from the initial dose. The patients received increasing doses of the extract, starting with one drop from vial 1 and increasing by one drop daily to 10 drops on the 10th day, following the graded course up to vial 4. The drops were taken sublingually in the morning before breakfast, kept sublingually for 1–2 min, and then swallowed with half cup of water. Maintenance therapy consisted of 10 drops daily and was reduced to three times per week after 6 months of therapy. The number of allergens used for immunization ranged from one to seven, but the test was initiated with the three highest reactive allergens, and the remaining allergens were given after reaching the maintenance dose.

Results

The two groups included in the study were as follows: group I included 20 asthmatic patients (13 male patients and seven female patients) with a mean age of 29.05 ± 8.27 years and group II included 20 asthmatic patients with allergic rhinitis (14 male patients and six female patients) with a mean age of 33.61 ± 6.43 years.

With respect to the clinical presentation of the studied patients in group I (Table 1), using the GINA score system, none of the patients (0%) had controlled asthma, 16 (80%) had partially controlled asthma, and four (20%) had poorly controlled asthma on average over the 30 days before scoring.

However, from the 20 asthmatic patients with allergic rhinitis in group II (Table 1), none of the patients (0%) had controlled asthma, 14 (70%) had partially controlled asthma, and six (30%) had poorly controlled asthma on average over the 30 days before scoring. When assessing the nasal condition using the ARIA score system, five patients (25%) had mild, 12 (60%) had moderate, and three (15%) had severe degrees of allergic rhinitis.

One year after SLIT, the clinical assessment of the patient's condition in group I with asthma (Table 2) was as follows: all (16) patients with partially controlled asthma showed improvement in their score after 1 year of treatment; the remaining four patients with poorly controlled asthma also showed improvement in their scores after 1 year, with three of them showing controlled asthma and one having partially controlled asthma; this patient had multiple allergies to several allergens.

In the clinical assessment of the condition of patients in group II with asthma and allergic rhinitis (Table 3), there was a correlation between the degree of control of asthma using the GINA and the severity of allergic rhinitis using the ARIA score – that is, the worse the GINA score, the worse the ARIA score. On reviewing the clinical condition after 1 year of SLIT, GINA asthma scoring revealed improvement in all patients. Fourteen patients who were partially controlled showed controlled asthma after 1 year of SLIT, and of the six patients with poor control five were controlled and one had a reduced score to partially controlled. The ARIA score showed that both patients with mild degree and those with moderate degrees of allergic rhinitis after 1 year had no symptoms of allergic rhinitis, and three patients with severe degree had only mild degree after 1 year of SLIT. To note, this was a patient with multiple allergies to several allergens.

With respect to the levels of eosinophil in blood, results revealed that, although there was an apparent

Table 1 Clinical presentation of the studied patients

Symptoms	*N* (%)	
	Asthmatic patients (*N* = 20)	Asthmatic patients with allergic rhinitis (*N* = 20)
Cough and expectoration	20 (100)	20 (100)
Dyspnea	17 (85)	14 (70)
Wheezy chest	11 (55)	9 (45)
Nocturnal asthma	8 (40)	12 (60)
Asthmatic attacks	11 (55)	12 (60)
Nasal symptoms		
Nasal obstruction	0 (0)	5 (25)
Sneezing	0 (0)	13 (65)
Rhinorrhea	0 (0)	16 (80)

Table 2 Distribution of reduction in clinical symptoms 1 year after sublingual immunotherapy in patients in the asthmatic group

	Asthmatic patients [*N* (%)]
Reduction in symptoms (*N*=20)	13 (65)
Reduction in nocturnal asthma (*N*=8)	7 (87.5)
Reduction in asthmatic attacks (*N*=11)	7 (63.63)
Reduction in need to rescue treatment (*N*=20)	14 (70)

Table 3 Distribution of reduction in clinical symptoms 1 year after sublingual immunotherapy in patients in the asthmatic with allergic rhinitis group

	Asthmatic patients with allergic rhinitis (*N* (%)]
Reduction in symptoms (*N*=20)	15 (75)
Reduction in nocturnal asthma (*N*=12)	11 (91.66)
Reduction in asthmatic attacks (*N*=12)	9 (75)
Reduction in need to rescue treatment (*N*=20)	15 (75)
Reduction in nasal symptoms (*N*=20)	13 (65)

Table 4 Distribution of blood eosinophils in asthmatic patients and asthmatic patients with allergic rhinitis before sublingual immunotherapy and 6 months and 1 year after the course of sublingual immunotherapy

	Before SLIT (mean ± SD)	6 months after SLIT (mean ± SD)	1 year after SLIT (mean ± SD)
Asthmatic patients (*N*=20)	321.45 ± 125.64	272.2 ± 86.74 *P*>0.05	232 ± 106.27 **P*<0.05
Asthmatic patients with allergic rhinitis (*N*=20)	345.65 ± 138.45	271.6 ± 141.79 *P*>0.05	217.05 ± 128.65 **P*<0.05

SLIT, sublingual immunotherapy.

reduction in levels 6 months after the initiation of therapy, these reductions were statistically insignificant in both groups, but on comparing levels of pretreatment with those 1 year after commencing SLIT there was a statistically significant decrease in blood eosinophils in both groups (Table 4). The reduction in the levels of eosinophils before treatment and after treatment was statistically comparable, and the levels were reduced by comparable degrees in both groups (Table 5).

With respect to the total IgE levels (Tables 6 and 7), there was statistically insignificant decrease in total IgE 6 months and 1 year after SLIT compared with that before the initiation of SLIT in the asthmatic patients group. However, there was a statistically insignificant decrease in total IgE 6 months after SLIT and a statistically significant decrease in total IgE 1 year after SLIT compared with that before SLIT in asthmatic patients with allergic rhinitis. With respect to the distribution of specific IgE to food and inhalants, the majority of patients in the asthmatic group before the initiation of SLIT were sensitive to three allergens (30%), followed by six allergens (15%), two allergens (15%), and one allergen (15%). One year after SLIT, the majority of patients were sensitive to zero allergens (35%), followed by one allergen (35%). However, the majority of patients in the asthmatic with allergic rhinitis group before initiation of SLIT were sensitive to six allergens (25%), followed by one allergen (25%), seven allergens (10%), five allergens (10%), four allergens (10%), and two allergens (10%). One year after SLIT, the majority of patients were sensitive to zero allergens (45%), followed by one allergen (20%). There was statistically significant reduction in the number of allergens from 3.65 ± 1.60 to 1.55 ± 1.27 in the asthmatic group and from 3.95 ± 2.11 to 1.35 ± 1.34 in the asthmatic with allergic rhinitis group ($P < 0.05$) 1 year after SLIT compared with that before SLIT (Table 8). The results of the skin prick test revealed that the majority of patients in the asthmatic group before initiation of SLIT were sensitive to three allergens (60%), followed by two allergens (20%). One year after SLIT, the majority of patients were sensitive to zero allergens (40%), followed by one allergen (40%). However, the majority of patients in the asthmatic with allergic rhinitis group were sensitive to three allergens (25%), followed by four allergens (20%). One year after SLIT, the majority of patients were sensitive to zero allergens (55%), followed by two allergens (20%). There was a statistically significant reduction in the number of allergens from 3.30 ± 1.30 to 0.55 ± 1.19 in the asthmatic group and from 4.1 ± 2.1 to 1.1 ± 1.33 in the asthmatic with allergic rhinitis group ($P < 0.05$) 1 year after SLIT compared with that before SLIT (Table 9). Our results revealed that the majority of patients in the asthmatic group were sensitive to mites (60%), followed by mixed grass pollens (30%), *Penicillium notatum* (25%), house dust (20%), and cockroach (20%). However, the majority of patients in the asthmatic with allergic rhinitis group were sensitive to mites (75%), followed by house dust (40%), mixed grass pollens (40%), mixed pollens (30%), cat epithelium (30%), *Penicillium notatum* (25%), cockroach (25%), dog epithelium (20%), and sheep wool (20%) (Table 10). Local reverse reactions (throat itching) were reported in one (5%) patient in the asthmatic group. No local side effects were reported in patients in the asthmatic with allergic rhinitis group. No systemic side effects were reported in either group.

Of the 20 patients in the asthmatic group, 13 patients (65%) tolerated SLIT very well, six (30%) showed good response, and one (5%) showed moderate response. However, 11 asthmatic patients with allergic rhinitis (55%) tolerated the therapy very well, seven patients (35%) showed good response, and two patients (10%) showed moderate response.

Table 5 Comparison of blood eosinophils in asthmatic patients vs. asthmatic patients with allergic rhinitis 1 year after the course of sublingual immunotherapy

	Mean ± SD	
	Asthmatic patients ($N = 20$)	Asthmatic patients with allergic rhinitis ($N = 20$)
Blood eosinophils	232 ± 106.27	217.05 ± 128.65 $P>0.05$

Discussion

Asthma and allergic rhinitis are characterized by common histopathologic and inflammatory cellular processes and appear to be manifestations of the same underlying disorder [13]. The common features of the two diseases suggest that symptoms of one may

Table 6 Results of total immunoglobulin E in patients in the asthmatic group and asthmatic with allergic rhinitis group before sublingual immunotherapy and 6 months and 1 year after the course of sublingual immunotherapy

	Before SLIT (mean ± SD)	6 months after SLIT (mean ± SD)	1 year after SLIT (mean ± SD)
Asthmatic patients ($N=20$)	1275.4 ± 949.73	635.89 ± 588.5 $P>0.05$	615.04 ± 469.8 $P>0.05$
Asthmatic patients with allergic rhinitis ($N=20$)	629.8 ± 485.48	461.19 ± 365.88 $P>0.05$	380.99 ± 312.76 $^{*}P<0.05$

ISLIT, sublingual immunotherapy.

impact symptoms of the other. In fact, the presence of concomitant allergic rhinitis in patients with asthma is associated with higher rates of asthma-related resource utilization and worsened asthma control [14]. Furthermore, therapy for allergic rhinitis can have a beneficial effect on asthma-related outcomes. Clinical trials have shown that treatment of allergic rhinitis can reduce asthma symptoms [14–16] and the need for emergency care for asthma [17].

Immunotherapy is the treatment that modifies the response of the immune system to allergens. It is considered a main line in the management of respiratory allergy. SLIT, which is administered in the form of drops underneath the tongue, has been widely utilized in Europe for the past 10 years. SLIT is now officially accepted as a viable alternative to the traditional subcutaneous route [11]. SLIT has received approval from the WHO working group and the international ARIA consensus group for use in patients with allergic rhinitis and asthma. The aim is to alleviate symptoms during exposure to the allergen. It is an FDA-approved, clinically effective method and induces long-term remission of allergic rhinitis and allergic asthma, with improvement in clinical symptoms [18,19].

Successful immunotherapy results not only in the increase in allergen concentration necessary to induce immediate or late-phase reactions but also in the decreased responses to nonspecific stimulation [20]. Therefore, in contrast to symptomatic treatment, it can reduce the likelihood of developing additional sensitizations by interrupting the so-called 'atopic march' and patients may benefit from persistence of alleviation of clinical symptoms [19–21]. SLIT induces a 10–100-fold increase in IgG1 and IgG4 and a modest increase in IgG2. It has been observed that IgG4 exerts inhibitory effects on binding of IgE–FcεRII complexes to B cells [22]. SLIT affects T-cell responses to allergen by employing several

Table 7 Comparison of total immunoglobulin E in patients in the asthmatic group vs. patients in the asthmatic with allergic rhinitis group 1 year after the course of sublingual immunotherapy

	Mean ± SD	
	Asthmatic patients (*N* = 20)	Asthmatic patients with allergic rhinitis (*N* = 20)
Total IgE	615.04 ± 469.8	380.99 ± 312.76 *P*>0.05

IgE, immunoglobulin E.

Table 8 Results of specific immunoglobulin E to food and inhalants in asthmatic patients and asthmatic patients with allergic rhinitis before and 1 year after the course of sublingual immunotherapy

	Asthmatic patients [*N* (%)]		Asthmatic patients with allergic rhinitis [*N* (%)]	
Specific IgE to food and inhalants	Before SLIT	1 year after SLIT	Before SLIT	1 year after SLIT
Specific IgE to 7 allergens	1 (5)	0 (0)	2 (10)	0 (0)
Specific IgE to 6 allergens	3 (15)	0 (0)	5 (25)	0 (0)
Specific IgE to 5 allergens	2 (10)	0 (0)	2 (10)	0 (0)
Specific IgE to 4 allergens	2 (10)	1 (5)	2 (10)	1 (5)
Specific IgE to 3 allergens	6 (30)	3 (15)	1 (5)	3 (15)
Specific IgE to 2 allergens	3 (15)	2 (10)	2 (10)	3 (15)
Specific IgE to 1 allergen	3 (15)	7 (35)	5 (25)	4 (20)
Specific IgE to 0 allergen	0 (0)	7 (35)	1 (5)	9 (45)
Total	20 (100)	20 (100)	20 (100)	20 (100)
Mean ± SD	3.65 ± 1.60	1.55 ± 1.27 *P<0.05	3.95 ± 2.11	1.35 ± 1.34 *P<0.05

IgE, immunoglobulin E; SLIT, sublingual immunotherapy.

Table 9 Results of skin prick test in asthmatic patients and asthmatic patients with allergic rhinitis before and 1 year after the course of sublingual immunotherapy

Skin prick test	Asthmatic patients [*N* (%)]		Asthmatic patients with allergic rhinitis [*N* (%)]	
	Before SLIT	1 year after SLIT	Before SLIT	1 year after SLIT
Positive test for 7 allergens	1 (5)	0 (0)	4 (20)	0 (0)
Positive test for 6 allergens	1 (5)	0 (0)	1 (5)	0 (0)
Positive test for 5 allergens	1 (5)	0 (0)	3 (15)	0 (0)
Positive test for 4 allergens	1 (5)	1 (5)	4 (20)	1 (5)
Positive test for 3 allergens	12 (60)	1 (5)	5 (25)	2 (10)
Positive test for 2 allergens	4 (20)	2 (10)	1 (5)	4 (20)
Positive test for 1 allergen	0 (0)	8 (40)	2 (10)	2 (10)
Positive test for 0 allergen	0 (0)	8 (40)	0 (0)	11 (55)
Total	20 (100)	20 (100)	20 (100)	20 (100)
Mean ± SD	3.3 ± 1.30	0.55 ± 1.19 *P<0.05	4.1 ± 2.1	1.1 ± 1.33 *P<0.05

SLIT, sublingual immunotherapy.

Table 10 Results of allergen sensitivity in asthmatic patients and asthmatic patients with allergic rhinitis

	N (%)	
	Asthmatic patients (*N* = 20)	Asthmatic patients with allergic rhinitis (*N* = 20)
House dust	4 (20)	8 (40)
Mites	12 (60)	15 (75)
Mixed grass pollens	6 (30)	8 (40)
Palm tree pollens	1 (5)	2 (10)
Rye pollens	2 (10)	2 (10)
Mixed pollens	3 (15)	6 (30)
Hay dust	0 (0)	1 (5)
Candida albicans	1 (5)	1 (5)
Aspergillus fumigatus	3 (15)	0 (0)
Penicillium notatum	5 (25)	0 (0)
Mixed moulds	2 (10)	0 (0)
Tobacco	1 (5)	2 (10)
Sheep epithelia	1 (5)	0 (0)
Goat epithelia	3 (15)	2 (10)
Camel epithelia	1 (5)	2 (10)
Cow epithelia	0 (0)	1 (5)
Dog epithelia	2 (10)	4 (20)
Cat epithelia	6 (30)	6 (30)
Horse hair	0 (0)	3 (15)
Pigeon	0 (0)	1 (5)
Shrimps	0 (0)	2 (10)
Cockroach	4 (20)	5 (25)
Sheep wool	0 (0)	4 (c20)
Peanuts	1 (5)	1 (5)
Hazelnuts	1 (5)	2 (10)
Milk	0 (0)	1 (5)
Egg yolk	1 (5)	1 (5)
Soya bean	1 (5)	1 (5)
Fish	1 (5)	2 (10)
Egg white	0 (0)	1 (5)
Shelfish	1 (5)	0 (0)
Banana	2 (10)	2 (10)

mechanisms: (a) increasing the allergen-induced ratio of TH1 cytokines to TH2 cytokines; (b) inducing epitope-specific T-cell anergy that can be blocked by neutralization of IL-10; (c) generating allergen-specific T-reg cells that can suppress the responses of effector T cells; and (d) increasing the production of cytokines with regulatory activity [23]. The most recent studies have shown that SLIT exerts a long-lasting effect up to 5 years after discontinuation, which can prevent the onset of new sensitizations [24].

In the present study, a trial has been conducted to administer SLIT using multiple allergens in allergic asthmatic patients with and without allergic rhinitis and to evaluate the clinical efficacy and safety of and changes in allergen-specific antibodies during SLIT and the subsequent impact on clinical control of both asthma and allergic rhinitis.

Our study revealed that there were statistically significant decreases in blood eosinophil levels 1 year after SLIT compared with that before SLIT in both the asthmatic group and the asthmatic with allergic rhinitis group. These results are in agreement with the findings of Kim *et al.* [25] who reported significant decrements in peripheral blood eosinophil counts in their allergic rhinitis patients treated with SLIT. In addition, La Grutta *et al.* [26] reported that the reduction in nasal eosinophils was statistically greater ($P<0.05$) only in the SLIT group. Our study revealed that there was a statistically insignificant decrease in total IgE 6 months and 1 year after SLIT compared with that before SLIT in the asthmatic patients group. However, there was a statistically insignificant decrease in total IgE 6 months after SLIT and a statistically significant decrease in total IgE 1 year after SLIT compared with that before SLIT in patients in the asthmatic with allergic rhinitis group (Table 5). This is in accordance with the study by Abd Elwadowd and Salem [27] who reported that the total IgE level (IU/ml) in allergic rhinitis patients before and after immunotherapy decreased from 789.24 ± 426.49 to 341.24 ± 227.15 IU/ml. The difference was found to be highly significant ($P < 0.001$). However, Kim *et al.* [25] reported that total IgE did not change significantly before and after SLIT in their studied patients.

Our studied asthmatic patients, with and without allergic rhinitis, had positive skin prick test results to one to seven allergens. Sixty percent of patients in the asthmatic group before initiation of SLIT were sensitive to three allergens with a mean number of 3.30 ± 1.30 allergens, and 25% of patients in the asthmatic with allergic rhinitis group were sensitive to three allergens with a mean number of 4.1 ± 2.1 allergens. This is similar to the study by Al-Shehri [28] who reported that the number of used allergens for immunization ranged from one to seven. For most of the patients, the use of two, three, or four allergens was reported (39 patients = 21.4%, 58 = 31.9%, 39 = 21.4%). For 17 patients (9.3%), only one allergen was needed, 10 patients (5.5%) used five allergens, and three patients used six and seven allergens, respectively. Wise *et al.* [29] reported that the mean number of antigens included in the SLIT regimens in their patient group was 11.6 (range, 3–21 antigens). In addition, Tripathi *et al.* [30] reported that allergens in graded strength having not more than five allergens were administered sublingually in all patients.

Our results revealed that the majority of patients in the asthmatic group were sensitive to mites (60%), followed by mixed grass pollens (30%), *Penicillium notatum* (25%), house dust (20%), and cockroach (20%). However, the majority of patients in the asthmatic with allergic rhinitis group were sensitive to mites (75%), followed by house dust (40%), mixed grass pollens (40%), mixed pollens (30%), cat epithelium

(30%), *Penicillium notatum* (25%), cockroach (25%), dog epithelium (20%), and sheep wool (20%) (Table 9). Abd Elwadowd and Salem [27] reported that dust mites represented 44% of the allergens; fungus allergens alone represented 12% of them; and mixed dust mites and fungus allergens represented 44% of cases. In addition, Tripathi *et al.* [30] reported that the most common allergens responsible for allergic asthma treated with SLIT using multiple allergens were house dust, house dust mites, pollen, and fungi.

Results of specific IgE to food and inhalants and the skin prick test revealed that there was a statistically significant reduction in the number of allergens 1 year after SLIT compared with that before initiation of SLIT in both the asthmatic group and the asthmatic with allergic rhinitis group ($P<0.05$). This is in agreement with the study by Tripathi *et al.* [30] who reported that allergen-specific IgE tested by the skin prick test showed significant reduction at the end of 3 years of SLIT. In addition, Bahceciler *et al.* [31] reported that total eosinophil count and specific IgE decreased significantly after treatment with SLIT compared with that in healthy controls.

With respect to the duration of SLIT, one patient (5%) in the asthma group discontinued treatment after 1 year, two (10%) after 18 months, three (15%) after 2 years because they felt free of symptoms, and 14 (70%) continued treatment for more than 2 years. Two patients (10%) in the asthma allergic rhinitis group discontinued treatment after 1 year, two (10%) after 18 months, four (20%) after 2 years because they felt free of symptoms, and 12 (60%) continued treatment for more than 2 years. Pajno *et al.* [32] reported that the discontinuation rate for SLIT after 12 months was 8.2%. In addition, Steiner *et al.* [33] reported that results of SLIT were equal 1, 3, and 5 years after termination of SLIT.

Side effects of SLIT in our study were very few and negligible. Local reverse reactions (throat itching) were reported in one (5%) patient in the asthma group. No local side effects were reported in patients in the asthmatic with allergic rhinitis group; this may be because allergic rhinitis patients often had throat irritation as part of their nasal and nasopharyngeal allergy syndrome. Hence, they did not attribute this to SLIT.

No systemic side effects were reported in either group. This is similar to the results of Wise *et al.* [29] who reported that there were no serious adverse events reported with the initiation of SLIT in their study. Similarly, Girado *et al.* [34] reported that the overall rate of all adverse events associated with the use of SLIT was very low at 1.4–4.9 events/1000 SLIT doses. In addition, Al-Shehri [28] reported reverse reactions in four patients (2.1%): one patient had systemic side effects, and three patients had local intolerance.

In our study, of the 20 asthmatic patients, 13 patients (65%) tolerated SLIT very well, whereas six (30%) showed good response and one showed (5%) moderate response. However, 11 asthmatic patients with allergic rhinitis (55%) tolerated therapy very well, whereas seven (35%) showed good response and two (10%) showed moderate response. These results were similar to that of Al-Shehri [28] who reported that, of the 182 documented patients, 125 (68.7%) tolerated therapy very well, 50 (27.5%) showed good response, four (2.2%) showed moderate response, and one patient (0.5%) showed poor response. In addition, Steiner *et al.* [33] reported that tolerability of SLIT was rated by 85% patients as 'excellent' and by 12% as 'good'; 3% of patients reported moderate side effects but no patient rated it as 'bad'.

Our results document improvement in asthma control in all patients in group I, as documented by improvement in the GINA score of all patients, even though it was of variable degree. In addition, the patients in group II had improvement in both control of asthma and allergic rhinitis when assessed using the GINA and ARIA scores, although the degrees of improvement in the GINA scores seemed better than ARIA scores 1 year after the course of SLIT. These results were similar to that of Bahceciler *et al.* [31] who reported significantly reduced asthma symptoms and medication use, reduced number of asthma exacerbations, increased forced expiratory volume in 1 s (FEV_1), and increased peak expiratory flow rate with SLIT. Similarly, Tripathi *et al.* [30] reported that the results of SLIT using multiple allergen showed significant reduction in symptoms and medication and improvement in PEFR by modifying the natural history of the disease and preventing the onset of new sensitization. In addition, Abramson *et al.* [35] reported a reduction in the need for medication, a reduction in bronchial hyper-responsiveness, and an improvement in FEV1 in a meta-analysis of allergen immunotherapy that included 75 prospective, randomized controlled trials of immunotherapy for asthma. Another meta-analysis of SLIT efficacy in the treatment of adult and pediatric allergic rhinitis by Wilson *et al.* [3] assessed 22 studies and found a statistically significant reduction in symptoms and in medication use, supporting the efficacy of SLIT in allergic rhinitis. Lue *et al.* [36] and Bahçeciler *et al.* [37] have reported significantly reduced asthma symptoms and medication use, reduced the number of asthma exacerbations, increased FEV_1, and increased peak expiratory flow rate with SLIT.

However, Ferrés *et al.*, [38] while studying the long-term effect of SLIT on asthma symptoms, found no reduction in the consumption of treatment for asthma between baseline and the 6-month visit. Furthermore, they did not find any improvement in asthma severity. The clinical condition of the patients in their study might explain the lack of significant improvement in asthma severity, as peak flow and FEV_1 at baseline were markedly high, indicating that asthma was well controlled in these patients when they initiated the treatment with SLIT. Wilson *et al.* [3] reported that, in patients who received SLIT, researchers observed a significant reduction in nasal obstruction, itching and cough, and a decreased need for medications for symptom relief. They also discovered that the patients who received SLIT made fewer trips to the physician's office and missed fewer days of work than those patients treated with only standard allergy/asthma medication.

Conclusion

From this study, we concluded that SLIT is a safe treatment strategy that significantly reduces symptoms and medication requirements and improves lung function in both asthmatic patients with and without allergic rhinitis. SLIT using multiple allergens lowered the allergen burden in both asthmatic patients with and without allergic rhinitis.

Limitations and recommendations

There are several limitations to our study. The first is the relatively small number of patients and the limited follow-up period of about 28 months. Second, most SLIT studies have used single allergen monotherapy to evaluate efficacy, whereas a few studies have included more than one allergen in the treatment regimen; hence, studies on the efficacy of monotherapy versus polytherapy in SLIT treatment regimens are lacking for comparison with our results. The third limitation is the lack of long-term follow-up of patients after 28 months to evaluate the long-term outcome of SLIT in these patients, which could be an aim of further studies.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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