Sublingual Versus Subcutaneous Immunotherapy as regards Efficacy and Safety in Respiratory Allergic Patients

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Subcutaneous immunotherapy (SCIT) is a well-established treatment modality for allergic patients that has been successfully used for many decades. Sublingual immunotherapy (SLIT) was introduced over the last 20 years as a safer alternative to SCIT with no single case of mortality has ever been reported with it. The aim of this study was to evaluate the efficacy and safety of SLIT versus SCIT in treating respiratory allergic patients. This study was a non-randomized controlled trial including 72 patients suffering from respiratory allergy to house dust mites (HDM) (Dermato-phagoidesfarinae and Dermato-phagoide-spteronyssinus) and date palm pollen (Phoenix dactylifera, Pho). The patients were subjected to full detailed allergy history taking, symptoms and medication scores calculation, skin prick test, Peak Expiratory Flow Rate (PEFR) for asthmatic patients, specific IgE test for HDM allergen. Patients received either SLIT or SCIT, then symptoms and medication scores, PEFR and specific IgE for HDM allergen were reassessed after 6 months of immunotherapy. Any adverse reactions were also recorded. The results showed that patients received either SLIT or SCIT showed a highly significant improvement in symptoms and medication scores with a highly significant improvement in PEFR, while specific IgE levels were not significantly changed. Local adverse reactions were noticed only with SCIT. We conclude that both modalities of treatment were equally effective in treatment of respiratory allergic patients to house dust mites and date palm pollen but SLIT had a more safety profile than SCIT.

Allergic disease is an increasingly prevalent problem affecting up to one-third of the general population in industrialized countries [1]. Respiratory allergies are the most common allergies in Europe and worldwide [2]. Allergic patients can benefit from immunotherapy as a treatment modality which can modify the immunological response to stop reacting to involved allergens [1]. Allergen immunotherapy (AIT) has the capacity to modify the natural course of disease by inducing long term immunological tolerance [3]. AIT is antigen specific, effective on multiple organs, efficient in asthma, rhinitis, provides long-lasting protection and is cost effective [4].

Immunotherapy can be administrated by different routes amongst which are injectable and oral vaccines. Injectable vaccines refer to classical subcutaneous immunotherapy (SCIT), usually known as allergy shots. Oral vaccines refer to sublingual immunotherapy where the allergens are administrated as drops to sublingual area, even though the term oral vaccines may also include allergy tablets [5].

Over the last two decades the European medical community approved high-quality evidence suggesting that sublingual immunotherapy (SLIT) is safer than SCIT with no single case of mortality has ever been reported with it [6,7].

The aim of this study was to evaluate the efficacy and safety of SLIT versus SCIT in treating different types of respiratory allergy.

Subjects, Materials and Methods

Subjects

This study was a nonrandomized controlled trial including 72 patients suffering from respiratory allergy, they were allergic to house dust mites (HDM) (*Dermato-phagoidesfarinae* and *Dermato-phagoidespteronyssinus)* and date palm pollen (*Phoenix dactylifera*Pho). They were recruited from the Allergy and Immunology Unit, Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University. Inclusion criteria: Patients (15-45 years) with respiratory allergy to HDM and date palm pollen, after his/her consent. Exclusion criteria: Patients <15years or >45 years of age, patient refusal, patients allergic to allergens other than HDM and date palm pollen, patients associated with skin allergy, severe persistent asthma, broncho-pulmonary disorders, infectious diseases, other respiratory or systemic diseases, patients on steroid-dependent treatment, pregnant females, smokers and patients on immunotherapy before the start of the study. The study protocol was reviewed and approved by the Institutional Review Board at the Faculty of Medicine, Zagazig University (approval no.: 2450, in 7 December 2015)

Materials and methods

The patients were divided into 3 groups of 24 patients each (A, Band C) suffering from rhinitis, asthma and combined asthma and rhinitis; respectively. Each group was re-divided into two subgroups, subgroup I received SLIT and subgroup II received SCIT. The selected patients were subjected to: full detailed allergy history taking, symptoms and medication scores calculation, skin prick test, Peak Expiratory Flow Rate (PEFR) for asthmatic patients, specific IgE test for HDM allergen at the baseline(before AIT administration). Patients received either SLIT or SCIT, then symptoms, medication scores, PEFR and specific IgE were reassessed after 6 months of immunotherapy and any adverse reactions were recorded.

1) Scoring:

a) Symptoms score: Recorded symptoms included nasal discharge, nasal obstruction, sneezing, cough, shortness of breath and wheezing. These were scored according to Fell's method with a numerical analog from 0 through 3 as follows:0 = symptom not present,1 = symptom was mild,2 = symptom was moderate,3 = symptom was severe [8,9]

b) Medication score

Medication use was also evaluated on a similar numerical scale as follows:0 = medication was not being used,1 = medication was being used once a week or less, 2 = medication was being used 2–3 times per week,3 = medication was being used 4 or more times per week [8,9].

2) Skin prick test:

Different Coca's extracted allergens were used from the Allergy and Immunology Unit, Medical Microbiology and Immunology Department, Faculty of Medicine, Zagazig University. Extracts were prepared as an aqueous glycerinated solution using the weight/volume unit. The allergen was eluted for a time, and then the solid material was filtered out, leaving an aqueous solution [9]. Allergens extracts were prepared under complete aseptic technique in the biological safety cabinet class II at the Allergy & Immunology Unit. The allergens tested were House dust mites, Date palm pollens, Smoke, Cotton, Mixed Fungi, Hay dust. The selected subjects were only sensitive to HDM and Date palm pollens. Readings and interpretations of the skin prick test were done according to (Dreborg, 2001; Bernstein *et al*, 2008) [10,11]

a) Technique:

Skin prick test was performed on the inner aspect of the forearm. The skin was disinfected by 70% ethyl alcohol and left to dry before test. Forearm was coded with a marker pen corresponding to the allergens being tested along with the positive control (Histamine dihydrochloride 10mg/ml) and negative control (saline). Marks were at least 2 cm apart. A drop of each allergen solution, negative and positive controls was placed beside each mark. A small prick through the drop was made to the skin using sterile prick lancet. After 15-20 minutes, the drops were wiped off and each wheal and flare were carefully outlined with a pen.

b) Time of reading results:

The histamine positive control result was read at 10-15 minutes after skin prick, while the results for allergens at 15-20 minutes [11]. Time was followed strictly because if the test was left longer than 20 minutes, the response might diminish or be lost.

c) Interpretation:

With a positive reaction to an allergen, the skin becomes itchy within a few minutes and then

becomes red and swollen with a wheal in the centre. A wheal of 3 mm or greater indicates the presence of specific IgE to the allergen tested and it clears for most people within an hour [10].

3) Peak Expiratory Flow Rate:

Material: Peak flow meter (Ferraris Respiratory).and PEFR chart to determine expected value for each patient depending on patient's gender, age and height.

Method: Steps for accurate recording and measurement of PEFR were performed according to the guidelines of National Asthma Education and Prevention Program [12].

4) Specific IgE for HDM:

Enzyme linked immunosorbent assay (ELISA) was used for the quantitative determination of specific IgE in human serum by (RIDASCREEN ® Spec. IgE, Art. No.:A0041, Germany) kit.

5) Allergen immunotherapy:

Sublingual Immunotherapy: Dilutions of allergens extracts were prepared using Glycerin 50% in 20 ml simple bottles with glassy dropper. Extracts were given as sublingual drops which were kept under the tongue for two minutes and then swallowed. The sublingual drops were administered in the morning on an empty stomach [13].SLIT was divided into two phases; the build-up and the maintenance phases [14]. During the build-up phase 3 increasing concentrations of the allergens were administrated (1/200 W/V, 1/100 W/V, 1/50 W/V) for 3 months, followed by the maintenance phase which started from the 4^{th} month (conc. 1/50 W/V) till the end of the 6^{th} month as indicated in Table (1).

Subcutaneous Immunotherapy: Dilutions of allergens extracts were prepared using saline (0.9%) in 10 ml vials. Allergen immunotherapy extract injections were administered with a 1-ml syringe. The injections were administered subcutaneously in the posterior portion of the middle third of the upper arm [14]. SCIT was divided into two phases; the build-up and the maintenance phases [14].During the build-up phase 5 increasing concentrations of the allergens were administrated (1/10000 W/V, 1/1000 W/V, 1/500 W/V, 1/250 W/V, 1/125 W/V) for 17 weeks, followed by the maintenance phase which started from the 18^{th} week (conc. 1/125 W/V) till the end of the 6 months of the administration period as recorded in Table (2).

6) Patient reassessment:

Symptoms and medication scores, PEFR and specific IgE were assessed after 6 months of immunotherapy.

Any adverse events were recorded for the patients using both modalities of treatment, including the following:

SLIT: Pruritis/swelling of mouth, tounge, or lips; throat irritation, nausea, abdominal pain, vomiting, diarrhea, heartburn, or uvular oedema.

SCIT: Local reactions common, occurs at the injection site, manifested primarily by wheal and flare with Pruritis, usually begins 20 to 30 minutes after injection.

Large local induration: It occurs at injection site, manifested by pain, tenderness, and hard swelling.

Systemic reactions: manifestations can include: urticaria, angioedema, increased respiratory symptoms (nasal or pulmonary), increased ocular symptoms, and hypotension.

Statistical Analysis

The data collected throughout history, basic clinical examination, laboratory investigations and outcome measures were analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 20.0) software for analysis. *P* values for calculated statistics tests were obtained. A *P* value <0.05 was considered statistically significant.

Table 1. Schedule of administration in SLIT.

Bottle	Conc.	Dose	Frequency	Duration	Period of treatment
RED (The first bottle)	1/200W/V	3 drops	Once daily	For the 1st 10 days	The 1st month
		5 drops		For the 2nd 10 days	
		7 drops		For the 3rd 10 days	
YELLOW (The second bottle)	1/100 W/V	3 drops		For the 1st 10 days	The 2nd month
		5 drops		For the 2nd 10 days	
		7 drops		For the 3rd 10 days	
GREEN (The third bottle)	1/50W/V	3 drops		For the 1st 10 days	The 3rd month
		5 drops		For the 2nd 10 days	
		7 drops		For the 3rd 10 days	
GREEN (The maintenance bottles)	1/50W/V	7 drops	Daily	For one month	The 4th month
		7 drops	3 times weekly	For two months	The 5th & 6th months

Table 2. Schedule of administration in SCIT.

Dose Conc	Doses/ ml										Frequency	Period of treatment
	1st	2nd	3rd	4th	5th	6th	7th	8th	9th	10th		
1/10000W/V	0.1	0.2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1	twice a week (doses were not repeated)	From the 1st to the end of 5th week
1/1000W/V					0.5	0.6	0.7	0.8	0.9	1		From the 6th to the 8th week
1/500W/V					0.5	0.6	0.7	0.8	0.9	1		From the 9th to the 11th week
1/250W/V					0.5	0.6	0.7	0.8	0.9	1		From the 12th to the 14th week
1/125 W/V					0.5	0.6	0.7	0.8	0.9	1		From the 15th to the 17th week
Maintenance (1/125 W/V)	1 ml										Weekly	From the 18th week till the end of 6th month

Results

The mean age of studied subjects was 29.33 ± 9.12 years in group A (Allergic rhinitis patients), 28.38 ± 9.08 years in group B (Bronchial asthma patients) and 29.92 ± 8.45 years in group C (combined asthma & rhinitis patients), with no significant difference between the three groups.

As regards gender distribution among the studied groups 10 (41.7%)) of the studied subjects were females and 14 (58.3%) were males in group A, 13 (54.2%) were females and 11 (45.8%) were males in group B and 10 (41.7%) were females and 14 (58.3%) were males in group C, with no significant difference between the three groups.

Patients received either SLIT or SCIT showed significant improvements in symptoms and medication scores in the three groups, with significant improvement in PEFR in group B and group C. However, specific IgE levels were insignificantly increased in patients received SLIT and insignificantly decreased in patients received SCIT. No statistically significant difference between the SLIT and SCIT before and 6 months after treatment as regards all the measured parameters, (Tables 1, 2 and 3).

Table 1. Comparison between mean symptoms score, mean medication score and mean levels of specific IgE before and 6 months after SLIT and SCIT treatment in group A (patients with allergic rhinitis) with comparison between SLIT and SCIT in this group using t/ Mann Whitney test.

Group A(Allergic rhinitis patients)		Mean ± SD	Paired t test *P* value	t/ Mann Whitney *P* value
Sublingual	Symptoms (before)	4.75±1.14	0.00	NS
	Symptoms (after)	2.25±0.75		NS
	Medication (before)	1.83±0.72	0.00	NS
	Medication (after)	0.75±0.62		NS
	Specific IgE(before)	1.40±0.89	NS	NS
	Specific IgE(after)	1.95±2.68		NS
Subcutaneous	Symptoms (before)	4.33±1.15	0.00	
	Symptoms (after)	1.58± 0.67		
	Medication (before)	2.00± 0.60	0.00	
	Medication (after)	0.83± 0.39		
	Specific IgE(before)	0. 90±1.05	NS	
	Specific IgE(after)	0.76± 0.81		

P>0.05 is not significant (NS)

Table 2. Comparison between mean symptoms score, mean medication score, mean levels of PEFR and mean levels of specific IgE before and 6 months after SLIT and SCIT treatment in group B (patients with bronchial asthma) with comparison between SLIT and SCIT in this group using t/ Mann Whitney test.

Group B (patients with bronchial asthma)		Mean ± SD	Paired t *P* value	t/ Mann Whitney *P* value
Sublingual	Symptoms (before)	4.75±1.14	0.00	NS
	Symptoms (after)	2.25±0.75		NS
	Medication (before)	2.17± 0.58	0.00	NS
	Medication (after)	1.25±0.45		NS
	PEFR (before)	398.33±65.93	0.00	NS
	PEFR (after)	462.50±70.73		NS
	Specific IgE(before)	1.42±0.87	NS	NS
	Specific IgE(after)	1.96±2.67		NS
Subcutaneous	Symptoms (before)	4.92±0.79	0.00	
	Symptoms (after)	2.50± 0.52		
	Medication (before)	2.50±0.52	0.00	
	Medication (after)	1.42±0.51		
	PEFR (before)	391.25±76.04	0.00	
	PEFR (after)	446.25±77.43		
	Specific IgE(before)	0.91 ± 1.04	NS	
	Specific IgE(after)	0.80 ± 0.79		

P>0.05 is not significant (NS)

Table 3. Comparison between mean symptoms score, mean medication score, mean levels of PEFR and mean levels of specific IgE before and 6 months after SLIT and SCIT treatment in group C (patients with allergic rhinitis and bronchial asthma) with comparison between SLIT and SCIT in this group using t/ Mann Whitney test.

Group C (patients with allergic rhinitis and bronchial asthma)		Mean±SD	Paired t *P* value	t/ Mann Whitney *P* value
Sublingual	Symptoms (before)	7.25±1.36	0.00	NS
	Symptoms (after)	3.42± 0.79		NS
	Medication (before)	2.58± 0.51	0.00	NS
	Medication (after)	1.42± 0.51		NS
	PEFR (before)	411.25±68.33	0.00	NS
	PEFR (after)	466.67±72.03		NS
	Specific IgE(before)	1.40± 0.89	NS	NS
	Specific IgE(after)	1.95±2.68		NS
Subcutaneous	Symptoms (before)	8.08±1.51	0.00	
	Symptoms (after)	3.83±1.27		
	Medication (before)	2.83±0.39	0.00	
	Medication (after)	1.58± 0.51		
	PEFR (before)	411.25±55.76	0.00	
	PEFR (after)	471.25±59.24		
	Specific IgE(before)	0.90±1.05	NS	
	Specific IgE(after)	0.75± 0.81		

P>0.05 is not significant (NS)

The adverse reactions recorded for the patients received either SLIT or SCIT, no side effects were detected with the SLIT treatment, but 6 patients (16.6%) suffered from local reactions at the injection site with the SCIT treatment. SLIT was significantly safer than SCIT (p= 0.025) by Fisher exact test, (Table 4).

Table 4. Adverse reactions detected in SLIT and SCIT treatment:

	SLIT	SCIT	*P* value
No. of patients (%) suffered from adverse reactions	0 (0.0%)	6 (16.6%)	0.025

Discussion

Allergic respiratory diseases (ARDs) are becoming an important public health problem and its prevalence is increased all over the world [15].Allergic rhinitis (AR) affects approximately 1 in each 5 individuals, whereas asthma affects between 1 and 18% of the general population [16]. ARDs have been associated with impaired quality of life and a high economic burden [17]. AIT is the only disease-modifying therapy, preventing the evolution of AR to asthma and its efficacy is confirmed in reducing asthma symptoms and medications, and improving airway hyper responsiveness [18]. Data for determining which administration route (subcutaneous immunotherapy [SCIT] or sublingual immunotherapy [SLIT] is more effective are currently insufficient [19].

In patients with allergic rhinitis(group A), there were lower mean symptoms score and lower mean medication score after 6 months of treatment by SLIT or SCIT compared to the pretreatment levels with a statistical significant difference. These findings were in consistence with Several published studies such as Durham *et al,* (2006), potter *et al.* (2015) and Feng *et al.*(2017)who concluded that SLIT provided a significant symptom relief and reduced the need for medications in allergic rhinitis patients [20,21,22]. Similarly, Purkey *et al.* (2013) and Lourenço *et al.* (2016) reported that SCIT as a treatment option for allergic rhinitis led to a reduction in all symptoms studied, improving the quality of life of patients, proving itself as an important therapeutic tool for these pathological conditions [23,24].

As regard the mean levels of specific IgE, there was no difference between pretreatment levels and 6 months after SLIT and SCIT treatments. This result is in agreement with Ahmadiafshar *et al.* (2013) who found that specific IgE levels did not change significantly after treatment by SLIT for 6 months [25]. However, this finding disagreed with result of Moreno *et al.*(2015) who performed a multi-centre clinical trial and observed a significant increase in specific IgE level after SCIT. This significant increase of IgE level could be explained by accelerated schedule of SCIT used with those patients as the maintenance dose was reached after only 5 weeks from the beginning of the treatment, while the maintenance dose was reached after 17 weeks in our current study [26].

Also, our finding is in contrary with Eifan *et al.,* (2010) who found a significant reduction in serum specific IgE levels one year after treatment by SLIT or SCIT. This difference may be due to different age group (children) who received a different regimen compared to our regimen and the specific IgE measured after a relatively longer duration [27].

In Comparison between sub-group I (SLIT) and subgroup II (SCIT) in patients with allergic rhinitis, there was no significant difference between the mean symptoms score and mean medication score ($p>0.05$) before and 6 months after treatment by both modalities of therapy. These findings are in agreement with Khinchi *et al.*

(2004) and Sayedelahl *et al.* (2015) [28,29]. Also, our results go in line with the standardized systematic review done by Dretzke *et al.* (2013) comparing the clinical effectiveness of SCIT and SLIT versus placebo. Both SCIT and SLIT provided equal significant reduction in symptoms score and medication use in case of adults and to lesser extent in children [30].

On the contrary, DiBona *et al.* (2012) reported that SCIT is more effective than SLIT in controlling symptoms and reducing the consumption of medications in seasonal allergic rhino conjunctivitis to grass pollen, but they performed an indirect comparison between SCIT and SLIT (they compared SCIT or SLIT with placebo) and they used different periods of therapy [31].

In Comparison between sub-group I (SLIT) and sub-group II (SCIT) in patients with allergic rhinitis as regard the mean level of specific IgE, there was no statistical significant difference between the two studied sub-groups before and 6 months after treatment (P>0.05).These results are in conflicting with Aasbjerg *et al.* 2014 who noticed that SLIT tablets induced initial 3 fold increase in specific IgE compared with SCIT after 3 months of treatment. This could be explained with exposure to relatively high doses of allergens during initiation of immunotherapy, especially with the sublingual route [32].

In patients with bronchial asthma (group B) there were significant lower mean symptoms score and significant lower mean medication score after 6 months of treatment by SLIT or SCIT compared to the pre-treatment levels.

Several published studies are in consistence with this results such as Hirsch *et al.* (1997), Bousquet *et al.* (1999), Basomba *et al,* (2002), Pifferi*et al.* (2002),Tsai *et al.*(2010) and Deb *et al.* (2012) [33,34,35.36.37,38].

In the contrary, Liao *et al.* (2015) were in partial agreement with the current result, they found SLIT significantly decreases asthma symptoms score with no significant change in medication score in asthmatic children receiving SLIT for one year, this difference could be explained by low doses of SLIT administrated to children, leading to delay of the clinical improvement and so no change in the medications use [39].

As regard the mean level of PEFR, there was a statistically high level of PEFR after 6 months of treatment by SLIT or SCIT in patients with bronchial asthma compared to pretreatment levels. This result is consistent with Torres Costa *et al.* (1996) and Saporta (2012) they constituted a retrospective study on patients with respiratory allergy receiving SLIT or SCIT for 6 months and showed a significant increase in PEFR values [40,41]. This result on the other hand, disagree with that of Niu*et al.* (2006) who performed a multi-center, randomized and placebo-controlled study and found no significant increase in PEFR. This may be due to the different regimen of therapy [42].

As regard the mean levels of specific IgE, there was no significant difference between the pretreatment levels and 6 months after receiving either SLIT or SCIT in bronchial asthma patients. These results are in agreement with LU *et al.* (1998) and Niu *et al.* (2006) they studied changes in specific IgE levels in asthmatic children received SLIT or SCIT. They found that specific IgE antibody level shows no significant change at the end of the study [43,44].

On the other hand, the present findings disagree with Hirsch *et al.* (1997) they detected a significant elevation of specific IgE level after 3 months and 12 month of SLIT to HDM sensitive asthmatic patients,

similarly, Martín-Muñoz *et al.* (2013) and Moreno *et al.,* (2015) reported a significant elevation in serum specific IgE levels in allergic asthmic patients after one year of SCIT [33,44,26].

In Comparison between sub-group I (SLIT) and sub-group II (SCIT) in patients with bronchial asthma as regards the mean symptoms score and mean medication score, there was no significant difference between the two studied sub-groups before and 6 months after treatment as regards the mean symptoms score and mean medication score ($p>0.05$), although there was a highly significant reduction of the mean symptoms score and mean medication score after 6 months in both modalities of therapy. The present results are in consistence with Omarjee & Tanguy (2010), Eifan *et al.* (2010), Saporta (2012) and Salah *et al.* (2017) who proved that there was no significant difference between both treatment modalities in reduction of symptoms and medication use [45,27,1,46].

On the other hand, these results are partially disagree with that of Mungan *et al.*(1999)who found that SCIT is more effective than SLIT in controlling asthma symptoms, while both of them had the same efficacy in decreasing the medications intake in adult asthmatic patients after 1 year of therapy [47].

In Comparison between sub-group I (SLIT) and sub-group II (SCIT) in patients with bronchial asthma as regards the mean level of PEFR, there was no significant difference between the two studied sub-groups before and 6 months after treatment ($P>0.05$), although both modalities showed a highly significant increase in PEFR after 6 months. These results agree with Saporta, (2012) who found that SLIT and SCIT were equally effective in achieving a significant increase in PEFR values [41].

The finding that there was no significant difference in the mean level of specific IgE before and 6 months after SLIT and SCIT treatments in patients with bronchial asthma is in agreement with Eifan *et al.* (2010)who proved that there was no significant difference between both treatment modalities in the mean level of specific IgE [27].

In patients with allergic rhinitis and bronchial asthma(group C) there were significant lower mean symptoms score and mean medication score after 6 months of treatment by SLIT or SCIT in the tested patients compared to pretreatment scores. These findings go in line with Tari *et al.* (1990), Incorvaia *et al.* (2010), Eifan *et al.* (2010) and Saporta (2012) who worked on patients with allergic rhinitis and bronchial asthma received SLIT or SCIT and found a significant decrease in both symptoms score and medication score [48,49,27,1].

As regard the mean levels of specific IgE, there was no significant difference between the pretreatment levels and 6 months after receiving either SLIT or SCIT in group C patients. These results are in agreement with Ebner *et al.* (1997) and Kim *et al.* (2014) they found that the level of specific IgE was not changed after one year of SCIT for respiratory allergic patients [50,51].On the other hand, Gomez *et al.* (2015) studied patients with rhino conjunctivitis and bronchial asthma underwent SLIT for 1-2 years and found that serum specific IgE was significantly decreased at the end of the treatment period [52].

The variations of IgE levels in different studies could be explained with many reasons such as; the regimen of administration and the amount of maintenance dose which were largely variable, the protocols of administration are

not standardized and the amount of major allergens remain largely variable.

In Comparison between sub-group I (SLIT) and sub-group II (SCIT) in patients with allergic rhinitis and bronchial asthma as regards the mean symptoms score and mean medication score, there was no significant difference between the two studied sub-groups before and 6 months after treatment ($P>0.05$), although there was a highly significant reduction of the mean symptoms score and mean medication score in both modalities. These results agree with Omarjee & Tanguy (2010) and Eifan *et al.* (2010), who reported that both modalities of treatment were highly effective in reducing symptoms score and medication use [45,27].

In comparison between sub-group I (SLIT) and sub-group II (SCIT) in patients with allergic rhinitis and bronchial asthma as regards the mean level of PEFR, there was no significant difference between the two studied sub-groups before and 6 months after treatment ($p>0.05$) although both modalities showed highly significant increase in PEFR after 6 months. These results go in line with Tari *et al.* (1990) and Saporta, (2012) who mentioned that both treatment modalities were equally effective in achieving a significant increase in PEFR values ($P < 0.001$) [48,41].

As regards the mean level of specific IgE in sub-group I (SLIT) and sub-group II (SCIT) in patients with combined allergic rhinitis and bronchial asthma, no difference between the two studied sub-groups before and 6 months after treatment that agree with Mungan *et al.* (1999) and Eifan *et al.* (2010). These studies proved that there was no significant difference between both treatment modalities as regard to the mean level of specific IgE [47,27].

As regard the adverse reactions recorded for the patients receiving AIT, SLIT was significantly safer than SCIT as no adverse reactions were detected with the SLIT group, but 6 of the patients in SCIT group (16.6%) suffered from local reactions at the injection site. This finding of better safety profile of SLIT over SCIT is consistent with Khinchi *et al.* (2004), Eifan *et al.* (2010) and James and Bernstein (2017) they noticed that SCIT may be associated with the risk of systemic reactions or even fatal anaphylaxis, while SLIT may be associated with local adverse reactions but the risk of anaphylaxis was very uncommon [28,27,53].

In conclusion, both modalities of treatment (SLIT and SCIT) were equally effective in treatment of respiratory allergic patients to house dust mites and date palm pollen, but SLIT had a more safety profile than SCIT.

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