Outcome of Sublingual Immunotherapy with Multiple Allergens in Asthmatic Patients with and without Allergic Rhinitis

Emara M.M.[1], Mansour H.A.[2], Shehata M.T.[3] and Zakia Abu-Zahab[4]

Departments of [1]Thoracic Medicine and [(2)]Clinical Pathology, Mansoura University
[3]Department of ENT, Ain Shams university
[4]Department of Clinical Pathology, Faculty Of Medicine For Girls, Al Azhar University, Egypt.
omima468@yahoo.com

Abstract: Background: Asthma is a chronic inflammatory pulmonary disorder that is characterized by reversible obstruction of the airways. Allergic rhinitis and allergic asthma are chronic inflammatory conditions that frequently co-exist, both with hallmark eosinophils. Immunotherapy is an established treatment of allergic diseases. Non-injective 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 the patients. Sublingual immunotherapy is now officially accepted as a viable alternative to the traditional subcutaneous route . **Aim of the work:** In the present study, a trial has been made to administer the sublingual immunotherapy using multiple allergens in allergic asthmatic Patients with and without allergic rhinitis and to evaluate the clinical efficacy, safety, and changes in allergen-specific antibodies during sublingual immunotherapy (SLIT). **Patients and methods:** This study was conducted at Kingdom of Saudi Arabia. The present study comprised two groups; group I included 20 asthmatic patients (13 males and 7 females) with a mean age of (29.05± 8.27 years). Group II included 20 male asthmatic patients with allergic rhinitis with a mean age of (33.61 ± 6.43 years). All patients were subjected to careful history taking and careful clinical examination, routine laboratory investigations, chest X ray PA, X ray paranasal sinuses, eosinophilic blood count and total IgE in serum by ELISA technique before start, after 6 months and after one year of the course of the sublingual immunotherapy, skin prick test and specific IgE to food and inhalants, Pulmonary function testing (spirometry) before start and after one year of the course of the sublingual immunotherapy**. Results**: Our results revealed that 8 out of 20 asthmatic patients group (40%) had nocturnal asthma and 11 patients (55%) had asthmatic attacks. On the other hand, 12 patients (60%) of asthmatic patients with allergic rhinitis had nocturnal asthma and asthmatic attacks**.** Our study revealed that, there were statistically significant decreases in blood eosinophils one year after SLIT compared to that before SLIT in both asthmatic patients with and without allergic rhinitis. Our study showed there were statistically insignificant decrease in total IgE in asthmatic patients group and statistically significant decrease in total IgE in asthmatic patients with allergic rhinitis one year after SLIT compared to that before SLIT. Results of specific IgE to food and inhalants revealed that, there were statistically significant reduction of number of allergens from 3.65±1.60 to 1.55±1.27 in asthmatic group and from 3.95±2.11to 1.35±1.34) in asthmatics with allergic rhinitis group (P<0.05) one year after SLIT compared to that before SLIT. Results of skin prick test revealed that, there were statistically significant reduction of number of allergens from (3.3**0±**1.30 to .55**±1.19)** in asthmatic group and from (4.1**±2.1** to 1.1**±1.33**) in asthmatics with allergic rhinitis group (P<0.05) one year after SLIT compared to that before SLIT. The majority of asthmatic patients group were sensitive to mites (60%), followed by mixed grass pollens (30%), *Penicillium notatum* (25%), house dust (20%), Cockroach (20%) respectively. On the other hand, the majority of asthmatic patients with allergic rhinitis group were sensitive to mites (75%), 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%). Results of Pulmonary function in both asthmatic patients group and asthmatic patients with allergic rhinitis showed statistically significant increase in FVC, FEV1, PEF, FEF25%, FEF50% and MVV one year after SLIT compared to that before SLIT. As regard the duration of sublingual immunotherapy one patient (5%) of asthma group discontinued treatment after one year, two (10%) after 18 months, 3 (15%) after 2 years, and 14 (70%) continue > 2 years. Two patients (10%) of asthma allergic rhinitis group discontinued treatment after one year, 2 (10%) after 18 months, 4 (20%) after 2 years, and 12 (60%) continue > 2 years. Local reverse reactions (throat itching) were reported in one (5%) patient of asthma group. No other local side effects or systemic side effects were reported in both asthmatic patients and asthmatic with allergic rhinitis group. From the twenty asthmatic group, 11 patients (55%) tolerated sublingual immunotherapy therapy very well, 7 (35%) good, 2 (10%) moderate. On the other hand, 10 asthmatic patients with allergic rhinitis (50%) tolerated therapy very well, 6 patients (30%) good, and 4 patients (20%) moderate. Our results revealed that 13 out of 20 (65%) asthmatic patients group had reduction of symptoms, 7 out of 8 patients (87.5%) had reduction of nocturnal asthma, 7 out of 11 patients (63.63%) had reduction of asthmatic attacks and 14 out of 20 patients (70%) had reduction of need to rescue treatment one year after the course of sublingual immunotherapy**.** On the other hand, 15 out of 20 (75%) asthmatic patients with allergic rhinitis group had reduction of

symptoms, 11 out of 12 patients (91.66%) had reduction of nocturnal asthma, 9 out of 12 patients (75%) had reduction of asthmatic attacks 15 out of 20 patients (75%) had reduction of need to rescue treatment, and 13 patients (65%) had reduction of nasal symptoms one year after the course of sublingual immunotherapy**. Conclusion:** From this study we concluded that sublingual immunotherapy is a safe treatment which significantly reduces symptoms and medication requirements, 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.
[Emara M.M., Mansour H.A., Shehata M.T. and Zakia Abu-Zahab. **Outcome of Sublingual Immunotherapy with Multiple Allergens in Asthmatic Patients with and without Allergic Rhinitis.** *Life Sci J* 2012;9(3):817-829]. (ISSN: 1097-8135). http://www.lifesciencesite.com. 116

Key words: Sublingual immunotherapy (SLIT) multiple allergens, Bronchial asthma, and Allergic rhinitis.

Abbreviations: Sublingual immunotherapy (SLIT), Allergic Rhinitis (AR).

1. Introduction:

Asthma is a chronic inflammatory pulmonary disorder that is characterized by reversible obstruction of the airways [(1)]. Allergic rhinitis is a common condition which, at its most severe, can significantly impair quality of life despite optimal treatment with antihistamines and topical nasal corticosteroids [(2)]. Allergic rhinitis and allergic asthma are chronic inflammatory conditions that frequently co-exist, both with hallmark eosinophils. Rhinitis or rhino sinusitis usually occurs in more than 75% of patients with allergic asthma and in more than 80% of patients with non allergic asthma, with reported percentages varying from 30 to 99% [(3)]. 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; in the middle range of the spectrum, rhinitis and AHR may be present; 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 via a systemic inflammatory response [(4)]. Immunotherapy is an established treatment of 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 [(5)]. Non-injective 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 the patients [(6)]. Sublingual immunotherapy is gaining widespread attention as a viable alternative to subcutaneous immunotherapy for the treatment of allergic rhino conjunctivitis. In addition, sublingual immunotherapy has been studied in other allergic disorders including asthma [(7)]. Sublingual immunotherapy (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 SCIT, which would allow for home administration [(5)]. The mechanism of action of both injection and sublingual immunotherapy remain under investigation, and injection immunotherapy has been proven to lead to long-term changes in the immunological response to allergen that may persist for years following discontinuation [(8)].

Aim of the work:

The purpose of this study was to evaluate the clinical efficacy, safety, and changes in allergen-specific antibodies during sublingual immunotherapy (SLIT) in asthmatic patients with and without allergic rhinitis.

2.Subjects and Methods:

This study comprised two groups; group I included 20 asthmatic patients with a mean age of (29.05± 8.27 years). Group II included 20 asthmatic patients with allergic rhinitis with a mean age of (33.61 ± 6.43 years) documented in a two-year follow-up study. The performance of the sublingual specific immunotherapy should last at least for 12 months. All patients were subjected to the following:

1. Careful history taking and clinical examination including age; sex; smoking habits; associated co-morbidity; onset of asthma, nocturnal worsening of asthma symptoms, frequency of asthmatic attacks, asthma medication needed, and asthma symptoms; dyspnea, cough, wheezy chest, nasal obstruction, rhinorrhea, sneezing, tolerability and duration of the sublingual immunotherapy, reduction of symptoms, asthmatic attacks and nocturnal asthma, and side effects experienced by the patients.
2. Chest X ray PA and x ray paranasal sinuses for asthmatic allergic rhinitis patients.
3. Routine laboratory investigations.

Eosinophilic blood count and total IgE in serum before start, after 6 months and after one year of the course of the sublingual immunotherapy. Total IgE: was determined using the By ELISA technique using a kit supplied by Bender Med Systems diagnostics (Bender Med systems Diagnostics, Vienna, Austria).

Expected range between 29-87 iu/ml according to age.

4. Skin-prick testing using battery containing 25 allergens was performed before start and after one year of the course of the sublingual immunotherapy. Patients should stop steroids and antihistaminic 48 hours before the test. Skin prick test was performed on the internal side of the forearms, with needle As follows:

- Clean arm with soap and water or alcohol
- The forearm is coded with a skin marker pen corresponding to the number of allergens being tested. Marks should be at least 2cm apart.
- A drop of allergen solution is placed beside each mark
- A small prick through the drop is made to the skin using a sterile prick lancet. A new lancet must be used for each allergen tested.
- Excess allergen solution is dabbed off with a tissue

Observe skin reactions – if a reaction occurs it should do so within 20-30 minutes In addition to the allergens tested, there should be a positive and negative control. The positive control, usually a histamine solution, should become itchy within a few minutes and then become red and swollen with a "wheal" in the centre. The negative control, usually a saline solution should show no response.

Skin prick testing results: There are a couple of grading scales used but the size of the wheal is most accurate. The size of the wheal does not indicate the severity of the symptoms but shows us the degree of sensitivity to the allergen.

Wheal size (mm)	Old "+" scale	Interpretation
<4	0+	Negative
5 – 10	2+	Mildly sensitive
10 – 15	3+	Moderately sensitive
>15	4+	Very sensitive

For skin prick tests to be informative they must be interpreted in conjunction with the patient's history and physical examination. The doctor must also be aware of the many reasons for a false-positive and false-negative reaction to properly interpret test

5. Specific IgE to food and inhalants in serum by RAST before start and after one year of the course of the sublingual immunotherapy. RAST by Using UniCAP 100ϵ , Pharmacia, for analyzing specific IgE in human serum detection limit of the CAP System is 0.35 kU/L and values greater than 0.35kU/L were considered positive

In principality, The CAP System FEIA employs a type of ''architecture'' wherebythe allergen of interest is covalently bound to a hydrophilic carrier polymer, encased in a capsule, which catches all allergen-specific IgE in the sample. Allergen-specific IgE is detected directly with a combination of polyclonal and monoclonal anti-IgE (Fc) antibodies labeled with beta-galactosidase, generating fluorescence.

The specific IgE antibody in the sample is connecting tto the allergens in the immunoCAP after buffer solution has been washed away (Pre-wash), all not connected sample is washed away (sample wash). Antibodies in the conjugate connects t to the IgE during conjugate incubation, excess conjugate is washed away in the conjugate wash. D evelopment solution is added and reacts with t the conjugate connected to the ImmunoCAP, After development incubation stop solution is added to halt the process. The volume is high (3x200µl), this is to flush the flourescent product down to the elution well for measurement.

6. Pulmonary function testing using computerized spirometry before start and after one year of the course of the sublingual immunotherapy.

All asthmatic patients had paroxysmal attacks of wheezy chest, dyspnea, cough and expectoration or documented reversible airway obstruction as determined by a 20% improvement in FEV1 after bronchodilator administration or Peak expiratory flow rate variability (>20%). Oral consent was taken from all patients before inclusion in this research. The choice of the allergen to be employed for SLIT should be made in accordance with the combination of clinical history and results of skin prick tests. Polysensitisation, i.e. the occurrence of multiple positive responses does not exclude SLIT, which may be done with the clinically most important allergens [(6)]. All significantly positive antigens (end point of ≥3) were included in each patient's SLIT treatment regimen. The performance of the sublingual specific immunotherapy should last at least for 12 months. No former specific immunotherapy was documented in any of the studied patients. Maintenance dosage was reached after six 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% glycerin I.P. was standardized according to w/v ratio of native material to the extracting fluid. Each course was provided in multi-dose 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
Maintenance Set: 1% w/v

Maintenance dose (strength 3) was recommended to be continued for three years. Dosage patterns were devised according to patient's sensitivity and tolerance. Care was taken to increase the dose at

regular intervals however; it could be increased provided the previous dose has been tolerated without any reaction. In case there was gap in treatment for more than two weeks, therapy was re-initiated (for safety reasons) with half of the dose last given. In the event of interruption of more than 4 weeks, the therapy was resumed from the initial dose. The patients received increasing doses of the extract, starting with 1 drop from vial 1 and increasing by one drop daily to 10 drops on the tenth day, following the graded course up to vial 4, the drops being taken sublingually in the morning before breakfast and being kept sublingually for 1-2 minutes and then swallowed with 1/2 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 used allergens for immunization ranged from 1 to 7 allergens.

3.Results:

This study comprised two groups; group I included 20 asthmatic patients (13 males and 7 females) with a mean age of (29.05± 8.27 years). Group II included 20 male asthmatic patients with allergic rhinitis with a mean age of (33.61 ± 6.43 years) (Table 1). As regard the clinical presentation of the studied patients, 20 asthmatic patients (100%) had cough & expectoration, 17 patients (85%) had dyspnea, 11 patients (55%) had wheezy chest, 8 patients (40%) had nocturnal asthma and 11 patients (55%) had asthmatic attacks. On the other hand, 20 asthmatic patients with allergic rhinitis (100%) had cough & expectoration, 14 patients (70%) had dyspnea, 9 patients (45%) had wheezy chest, 12 patients (60%) had nocturnal asthma and asthmatic attacks, 5 patients (25%) had nasal obstruction , 13 patients (65%) had sneezing and 16 patients (80%) had rhinorrhea **(Table 2).** Our study revealed that, there were statistically insignificant decrease in blood eosinophils 6 months after SLIT and statistically significant decrease in blood eosinophils one year after SLIT compared to that before SLIT in both asthmatic patients and asthmatic patients with allergic rhinitis **Table (3)**. Our study revealed that, there were statistically insignificant decreases in blood eosinophils one year after SLIT in asthmatic patients with allergic rhinitis compared to asthmatic patients group (**Table 4)**. **Table (5)** showed, there were statistically insignificant decrease in total IgE 6 months and one year after SLIT compared to that before start of SLIT in asthmatic patients group. On the other hand, there were statistically insignificant decreases in total IgE 6 months after SLIT and statistically significant decrease in total IgE one year after SLIT compared to that before SLIT in asthmatic patients with allergic rhinitis. Our study showed statistically insignificant decrease in total IgE one year after SLIT in asthmatic patients with allergic rhinitis group compared to asthmatic patients group **Table (6)**. As regard to distribution of specific IgE to food and inhalants, the majority of asthmatic patients group before start of SLIT were sensitive to 3 allergens (30%) followed by 6 allergens (15%), 2 allergens (15%), and one allergen (15%) respectively. One year after SLIT, the majority were sensitive to 0 allergen (35%) followed by one allergen (35%). On the other hand, the majority of asthmatic patients with allergic rhinitis group before start of SLIT were sensitive to 6 allergens (25%) followed by one allergen (25%), 7 allergens (10%), 5 allergens (10%), 4 allergens (10%), and two allergens (10%) respectively. One year after SLIT, the majority were sensitive to 0 allergen (45%) followed by one allergen (20%)**.** There were statistically significant reduction of number of allergens from 3.65±1.60 to 1.55±1.27 in asthmatic group and from 3.95±2.11to 1.35±1.34) in asthmatics with allergic rhinitis group (P<0.05) one year after SLIT compared to that before SLIT **(Table 7**). The results of skin prick test revealed that, the majority of asthmatic patients group before start of SLIT were sensitive to 3 allergens (60%) followed by 2 allergens (20%) respectively. One year after SLIT, the majority were sensitive to 0 allergen (40%) followed by one allergen (40%). On the other hand, the majority of asthmatic patients with allergic rhinitis group were sensitive to 3 allergens (25%) followed by 4 allergens (20%) respectively. One year after SLIT, the majority were sensitive to 0 allergen (55%) followed by 2 allergens (20%). There were statistically significant reduction of number of allergens from (3.3**0±**1.30 to .55**±1.19)** in asthmatic group and from (4.1**±2.1** to 1.1**±1.33**) in asthmatics with allergic rhinitis group (P<0.05) one year after SLIT compared to that before SLIT **(Table 8)**. Our results revealed that the majority of asthmatic patients group were sensitive to mites (60%), followed by mixed grass pollens (30%), *Penicillium notatum* (25%), house dust (20%), Cockroach (20%) respectively. On the other hand, the majorities of asthmatic patients 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%) (Table9). As regard the distribution of drug therapy in asthmatic patients 20 patients (100%) received combined LABA and inhaled steroids, 4 patients (20%) received theophylline, 5 patients (25%) received leukotriene modifiers and one patient (5%) received systemic steroids. 20 patients (100%) of asthmatic allergic rhinitis group received combined LABA and inhaled steroids, 4 patients (20%) received leukotriene modifiers and two patients (10%) received systemic steroids and 20 patients (100%) received topical nasal steroids **(Table10)**. As regard the results of pulmonary function in both asthmatic patients group and asthmatic

patients with allergic rhinitis, there were statistically significant increase in FVC, FEV1, PEF, FEF25%, FEF50% and MVV and statistically insignificant increase in FEF75% one year after SLIT compared to that before SLIT **(Table11).** Our study revealed that, there were statistically significant increase in FEV1, and MVV and statistically insignificant increase in FVC, PEF, FEF25%, FEF50% and FEF75% in asthmatic patients with allergic rhinitis group one year after SLIT compared to that in asthmatic patients group **Table (12).** As regard the duration of sublingual immunotherapy one patient (5%) of asthma group discontinued treatment after one year, two (10%) after 18 months, 3 (15%) after 2 years, and 14 (70%) continue > 2 years. Two patients (10%) of asthma allergic rhinitis group discontinued treatment after one year, 2 (10%) after 18 months, 4 (20%) after 2 years, and 12 (60%) continue > 2 years **(Table 13)**. Local reverse reactions (throat itching) were reported in one (5%) patient of asthma group. No local side effects were reported in asthmatic patients with allergic rhinitis group. No systemic side effects were reported in both groups **(Table 14).** From the twenty asthmatic group, 13 patients (65%) tolerated sublingual immunotherapy therapy very well, 6 (30%) good, 1 (5%) moderate. On the other hand, 11 asthmatic patients with allergic rhinitis (55%) tolerated therapy very well, 7patients (35%) good, 2 patients (10%) moderate **(Table 15)**. Our results revealed that 13 out of 20 (65%) asthmatic patients group had reduction of symptoms, 7 out of 8 patients (87.5%) had reduction of nocturnal asthma, 7 out of 11 patients (63.63%) had reduction of asthmatic attacks and 14 out of 20 patients (70%) had reduction of need to rescue treatment one year after the course of sublingual immunotherapy **(Table 16).** On the other hand, 15 out of 20 (75%) asthmatic patients with allergic rhinitis group had reduction of symptoms, 11 out of 12 patients (91.66%) had reduction of nocturnal asthma, 9 out of 12 patients (75%) had reduction of asthmatic attacks, 15 out of 20 patients (75%) had reduction of need to rescue treatment, and 13 patients (65%) had reduction of nasal symptoms one year after the course of sublingual immunotherapy **(Table 17).**

Table (1): Age and Sex distribution among the studied patients.

GROUP	AGE M ± SD	Minimal	Maximal	SEX			
				Males		Females	
				No.	%	No.	%
Asthmatic patients. No. = 20	27.9± 11.63	14	50	13	65	7	35
Asthmatic patients with allergic rhinitis. No. = 20	31.75 ± 9.16	15	49	20	100	0	0

Table (2): Clinical presentation of the studied patients.

Symptoms	Asthmatic patients. No= 20		Asthmatic patients with allergic rhinitis. No=20	
	No.	%	No.	%
Cough & 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 (3): Distribution of blood eosinophils in asthmatic patients and asthmatic patients with allergic rhinitis before, 6 months and one year after the course of sublingual immunotherapy.

	Before SLIT. M ± SD	6 months after SLIT. M ± SD	One year after SLIT. M ± SD
Asthmatic patients. No= 20	321.45 ± 125.64	272.2 ± 86.74 ***P* > 0.05**	232 ± 106.27 * ***P* < 0.05**
Asthmatic patients with allergic rhinitis. No=20	345.65 ± 138.45	271.6 ± 141.79 ***P* > 0.05**	217.05 ± 128.65 * ***P* < 0.05**

Table (4): Comparison of blood eosinophils in asthmatic patients versus asthmatic patients with allergic rhinitis one year after the course of sublingual immunotherapy.

	Asthmatic patients. No= 20; M ± SD	**Asthmatic patients with allergic rhinitis. No=20 M ± SD**
Blood eosinophils	232 ± 106.27	217.05 ± 128.65; ***P* > 0.05**

Table (5): Results of total IgE in asthmatic patients group and asthmatic patients with allergic rhinitis before, 6 months and one year after the course of sublingual immunotherapy.

	Before SLIT. M ± SD	**6 months after SLIT. M ± SD**	**One year after SLIT. M ± SD**
Asthmatic patients. No= 20	949.73 ± 1275.4	588.5 ± 635.89 **P > 0.05**	469.8 ± 615.04 **P > 0.05**
Asthmatic patients with allergic rhinitis. No=20	629.8 ± 485.48	461.19 ± 465.88 **P > 0.05**	312.76 ± 380.99 *** P < 0.05**

Table (6): Comparison of total IgE in asthmatic patients group versus asthmatic patients with allergic rhinitis one year after the course of sublingual immunotherapy.

	Asthmatic patients. No= 20; M ± SD	**Asthmatic patients with allergic rhinitis. No=20 M ± SD**
Total IgE	469.8 ± 615.04	312.76 ± 380.99; **P > 0.05**

Table (7): Results of specific IgE to food and inhalants in asthmatic patients and asthmatic patients with allergic rhinitis before and one year after the course of sublingual immunotherapy.

Specific IgE to food and inhalants.	**Asthmatic patients**				**Asthmatic patients with allergic rhinitis**			
	Before SLIT.		**One year after SLIT.**		**Before SLIT.**		**One year after SLIT.**	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
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 one 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	

Table (8): Results of skin prick test results in asthmatic patients and asthmatic patients with allergic rhinitis before and one year after the course of sublingual immunotherapy.

Skin prick test	**Asthmatic patients**				**Asthmatic patients with allergic rhinitis**			
	Before SLIT.		**One year after SLIT.**		**Before SLIT.**		**One year after SLIT.**	
	No.	**%**	**No.**	**%**	**No.**	**%**	**No.**	**%**
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 one 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		.55±**1.19** * *P* < 0.05		4.1±**2.1**		1.1±**1.33** * *P* < 0.05	

Table (9): Results of allergen sensitivity in asthmatic patients and asthmatic patients with allergic rhinitis.

	Asthmatic patients No =20		Asthmatic patients with allergic rhinitis No =20	
	No.	%	No.	%
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 fumigates	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 epith.	1	5	2	10
Cow epith.	0	0	1	5
Dog epith.	2	10	4	20
Cat epith.	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	20
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

Table (10): Distribution of drug therapy in asthmatic patients group and asthmatic patients with allergic rhinitis.

Duration of treatment	Asthmatic patients. No= 20		Asthmatic patients with allergic rhinitis. No=20	
	No.	%	No.	%
• Combined (LABA) and inhaled steroids.	20	100	20	100
• Theophylline.	4	20	0	0
• Leukotriene modifiers.	5	25	4	20
• Systemic steroids.	1	5	2	10
• Topical nasal steroids.	0	0	20	100

Table (11): Results of pulmonary function in asthmatic patients and asthmatic patients with allergic rhinitis before and one year after SLIT.

Pulmonary Function Data.	Asthmatic patients No. = 20		Asthmatic patients with allergic rhinitis No. = 20	
	Before SLIT. M ± SD	One year after SLIT. M ± SD	Before SLIT M ± SD	One year after SLIT. M ± SD
FVC.	78.68±6.04	88.35 ± 5.01 * P < 0.05	79.45 ± 15.74	89.10 ± 5.39 * P < 0.05
FEV1.	67 ± 13.21	81.15 ± 7.53 * P < 0.05	70.4 ± 15.37	86.5 ± 5.88 * P < 0.05
PEF.	58.1 ± 13.45	78.1 ± 9.97 * P < 0.05	64.6 ± 18.81	79.85 ± 9.19 * P < 0.05

FEF25%	57.65 ± 15.49	69.6 ± 9.57 * *P* < **0.05**	64.55 ± 18.43	74.9 ± 11.29 * *P* < **0.05**
FEF50%	59.15 ± 15.05	69.65 ± 11.84 * *P* < **0.05**	63.9 ± 19.89	76.9 ± 11.99 * *P* < **0.05**
FEF75%	60.3 ± 20.25	68.8 ± 14.84 *P* > **0.05**	68.4 ± 25.08	77.75 ± 15.08 *P* > **0.05**
MVV	63.25 ± 12.57	80.05 ± 7.27 * *P* < **0.05**	71.85 ± 16.6	86.6 ± 7.56 * *P* < **0.05**

Table (12): Comparison of pulmonary function data in asthmatic patients group versus asthmatic patients with allergic rhinitis one year after the course of sublingual immunotherapy (SLIT).

Pulmonary Function Data.	Asthmatic patients. No. = 20; M ± SD	Asthmatic patients with allergic rhinitis. No. = 20; M ± SD
FVC.	88.35 ± 5.01	89.10 ± 5.39 *P* > **0.05**
FEV1.	81.15 ± 7.53	86.5 ± 5.88 * *P* < **0.05**
PEF.	78.1 ± 9.97	79.85 ± 9.19 *P* > **0.05**
FEF25%	69.6 ± 9.57	74.9 ± 11.29 *P* > **0.05**
FEF50%	69.65 ± 11.84	76.9 ± 11.99 *P* > **0.05**
FEF75%	68.8 ± 14.84	77.75 ± 15.08 *P* > **0.05**
MVV	80.05 ± 7.27	86.6 ± 7.56 * *P* < **0.05**

Table (13): Distribution of duration of sublingual immunotherapy (SLIT) in asthmatic patients and asthmatic patients with allergic rhinitis.

Duration of treatment	Asthmatic patients		Asthmatic patients with allergic rhinitis	
	No.	%	No.	%
One year.	1	5	2	10
18 months	2	10	2	10
2 years.	3	15	4	20
> 2 years	14	70	12	60
Total	20	100	20	100

Table (14): Distribution of side effects of sublingual immunotherapy (SLIT) in asthmatic patients and asthmatic patients with allergic rhinitis.

Side effects	Asthmatic patients. No= 20		Asthmatic patients with allergic rhinitis. No=20	
	No.	%	No.	%
• **Nausea.**	0	0	0	0
• **Mouth itching or burning.**	0	0	0	0
• **Throat itching.**	1	5	0	0
• **Systemic reaction.**	0	0	0	0
Total	1	5	0	0

Table (15): Distribution of tolerability of sublingual immunotherapy (SLIT) in asthmatic patients and asthmatic patients with allergic rhinitis.

Tolerability	Asthmatic patients.		Asthmatic patients with allergic rhinitis.	
	No.	%	No.	%
Very well	13	65	11	55
Good	6	30	6	30
Moderate	1	5	1	20
Bad	0	0	0	0
Total	20	100	20	100

Table (16): Distribution of reduction of clinical symptoms one year after (SLIT) in asthmatic patients group.

	Asthmatic patients.	
	No.	**%**
• **Reduction of symptoms No= 20.**	13	65
• **Reduction of nocturnal asthma No = 8.**	7	87.5
• **Reduction of asthmatic attacks No= 11.**	7	63.63
• **Reduction of need to rescue treatment No = 20.**	14	70

Table (17): Distribution of reduction of clinical symptoms one year after (SLIT) in asthmatic patients with allergic rhinitis group.

	Asthmatic patients with allergic rhinitis.	
	No.	**%**
• **Reduction of symptoms No= 20.**	15	75
• **Reduction of nocturnal asthma No = 12.**	11	91.66
• **Reduction of asthmatic attacks No= 12.**	9	75
• **Reduction of need to rescue treatment No = 20.**	15	75
• **Reduction of nasal symptoms No = 20.**	13	65%

4.Discussion:

Asthma and allergic rhinitis are characterized by common histopathological and inflammatory cellular processes and appear to be manifestations of the same underlying disorder [9]. The common features of the two diseases suggest that symptoms of one may 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 [10]. Moreover, 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 [10-12]. and emergency care for asthma [13]. Immunotherapy is the treatment that modifies the response of the immune system to allergens. It is considered a cornerstone in the management of respiratory allergy. Sublingual immunotherapy (SLIT), which is administered in the form of drops underneath the tongue, has been widely utilized in Europe for the past 10 years. Sublingual immunotherapy is now officially accepted as a viable alternative to the traditional subcutaneous route [14]. Sublingual immunotherapy (SLIT) has received approval from WHO working group and the international ARIA (Allergic rhinitis and its impact on asthma) 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 [15,16].

Successful immunotherapy results not only in the increase of allergen concentration necessary to induce immediate or late-phase reactions, but also in the decreased responses to nonspecific stimulation [17]. 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 [15,17,18]. SLIT induces ten to hundred fold increase in IgG1 and -4 and a modest increase in IgG2. It has been observed that IgG4 exerts inhibitory effects on binding of IgE-FcεRII complexes on B cells [19]. SLIT affects T-cell responses to allergen by employing several mechanisms, including the following: by increasing the allergen-induced ratio of TH1 cytokines to TH2 cytokines, by inducing epitope-specific T-cell anergy that can be blocked by neutralization of IL-10, by generating allergen-specific T reg cells that can suppress the responses of effector T cells and by increasing the production of cytokines with regulatory activity [20]. The studies have shown that sublingual immunotherapy exerts a long-lasting effect up to 5 years after discontinuation and that it is able to prevent the onset of new sensitizations [21]. In the present study, a trial has been made to administer the sublingual immunotherapy using multiple allergens in allergic asthmatic Patients with and without allergic rhinitis and to evaluate the clinical efficacy, safety, and changes in allergen-specific antibodies during sublingual immunotherapy (SLIT). Our study revealed that(40%) of asthmatic patients group and (60%) of asthmatic patients with allergic rhinitis group had nocturnal asthma **(Table 2).** This is in agreement with **Storms *et al.*, 1994** [22]. who reported that a total of 204 out of their 304 studied patients (67%) had nocturnal symptoms of asthma. Our study revealed that there were statistically significant decrease in blood eosinophils one year after SLIT compared to that before SLIT in both asthmatic patients group and asthmatic patients with allergic rhinitis group **Table (3)**. **Kim *et al.*, 2010** [23] reported that there were

significant decrements in peripheral blood eosinophil counts and ECP (p = 0.025 and p = 0.048, respectively) in their allergic rhinitis patients treated with SLIT. Also, **La Grutta *et al.*,2007** [24] reported that the reduction of nasal eosinophils was statistically greater (p < 0.05) only in the SLIT group. Our study revealed that, there were statistically insignificant decrease in total IgE 6 months and one year after SLIT compared to that before SLIT in asthmatic patients group. On the other hand, there were statistically insignificant decrease in total IgE 6 months after SLIT and statistically significant decrease in total IgE one year after SLIT compared to that before SLIT in asthmatic patients with allergic rhinitis group **(Table 5)**. This is in accordance to **Abd Elwadowd, and Salem, 2005**[25] who reported that the total IgE level (iu/ml) in allergic rhinitis patients before and after immunotherapy decreased from789.24 ± 426.49 to 341.24 ±227.15 iu/ml. The difference was found to be highly significant (P<0.001). On the other hand, **Kim *et al.*, 2010** [23] reported that total IgE did not change significantly before and after SLIT of their studied patients. Our studied asthmatics with and without allergic rhinitis had positive skin prick test ranged from 1 to 7 allergens. Sixty percent of asthmatic group before start of SLIT were sensitive to 3 allergens with a mean number of 3.3**0**±1.30 allergens., and (25%) of asthmatic patients with allergic rhinitis group were sensitive to 3 allergens with a mean number of 4.1**±2.1** allergens. This is similar to the study of **Al-Shehri, 2002** [26] who reported that the number of used allergens for immunisation ranged from 1 to 7 allergens. For most of the patients the use of 2, 3 or 4 allergens was reported (39patients = 21.4 %, 58 = 31.9 %, 39 = 21.4 %). For 17 patients (9.3 %) only one allergen was needed, 10 patients (5.5 %) used 5 allergens and 3 patients used 6 and 7 allergens respectively. **Wise *et al.*, 2009** [27] reported that the mean number of antigens included in SLIT regimens in their patient group was 11.6 (range, 3-21 antigens). Also, **Tripathi *et al.*,2008** [28] reported that allergens in graded strength having not more than 5 allergens were administered sublingually in all the patients. Our results revealed that the majority of asthmatic patients group were sensitive to mites (60%), followed by mixed grass pollens (30%), Penicillium notatum (25%), house dust (20%), Cockroach (20%) respectively. On the other hand, the majority of asthmatic patients 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, 2005** [25] reported that the dust mites allergens represented (44%) of the group; fungus allergens alone represented (12%) of them while Mixed Dust mites and Fungus allergens represent 44% of cases. Also, **Tripathi *et al.*,2008** [28] 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 skin prick test revealed that there were statistically significant reduction of number of allergens one year after SLIT compared to that before start of SLIT in both asthmatic group and asthmatic with allergic rhinitis group (P<0.05). This is in agreement with **Tripathi *et al.*, 2008** [28] who reported that allergen specific IgE tested by skin prick test showed significant reduction at the end of three years of SLIT. Also, **Bahceciler *et al.*, 2005** [29] reported that total eosinophil count and specific IgE decreased significantly after treatment with SLIT compared to that of healthy controls. Results of Pulmonary function in both asthmatic patients group and asthmatic patients with allergic rhinitis showed statistically significant increase in FVC, FEV1, PEF, FEF25%, FEF50% and MVV one year after SLIT compared to that before SLIT **(Table 11).** This is in accordance to **Wise *et al.*, 2009** [27] who reported that increases in forced expiratory volume in 1 second (FEV1), mean expiratory flow at 25% of forced vital capacity (FVC), and methacholine threshold dose in adult patients treated with SLIT for birch pollen allergy. Also**, Calamita *et al.*, 2006** [30] reported in a systematic review of randomized-clinical trials using the Cochrane Collaboration method that among the respiratory function tests evaluated (FEV1, FEV1%, PEF, and FEF25–75%), FEV1% showed a significant improvement (SMD 1.48; 95% CI: 0.13–2.82), among 144 patients in four studies (54, 55, 60, 66) and FEF25–75% (SMD 1.06; 95% CI: 0.40–1.72) among 42 patients in two studies (54, 66); the values in these studies, which are greater than zero, indicated that treatment by SLIT was favored. As regard the duration of sublingual immunotherapy one patient (5%) of asthma group discontinued treatment after one year, two (10%) after 18 months, 3 (15%) after 2 years because they felt free of symptoms, and 14 (70%) continued > 2 years. Two patients (10%) of asthma allergic rhinitis group discontinued treatment after one year, 2 (10%) after 18 months, 4 (20%) after 2 years because they felt free of symptoms, and 12 (60%) continued > 2 years **(Table 13)**. **Pajno *et al.*, 2005** [31] reported that the discontinuation rate for SLIT after 12 months was 8.2%. Also, **Steiner *et al.*, 2009** [32] reported that results of SLIT were equal 1, 3 and 5 years after termination of SLIT. Side effects of SLIT in our study was very few and negligible. Local reverse reactions (throat itching) were reported in one (5%) patient of asthma group. No local side effects were reported in asthmatic patients with allergic rhinitis group. No systemic side effects were reported in both

groups **(Table 14).** This is similar to the results of **Wise** ***et al.,*** **2009** [27] who reported that there were no serious adverse events reported with the initiation of SLIT at their study. Similarly, **Girado** ***et al.,*** **2005**[33] reported that the overall rate of all adverse events associated with the use of SLIT was very low at 1.4 to 4.9 events per 1000 SLIT doses. Also, **Al-Shehri,2002**[26] reported reverse reactions were reported in 4 cases (2.1 %), one case with systemic side effects and 3 cases with local intolerance. Adverse reactions were described as burning sensation and itching in the mouth as well as nausea, severe throat smarting and scraping. Upon passing through a too fast dosistitration one patient reported allergic symptoms like conjunctivitis, rhinitis and aggravated asthma, which longed for a reduction and adjusted doses titration in future. Dilution of 1:10 and a slow doses titration resulted in good tolerance. For one patient the adverse reactions were not specified. From the twenty asthmatic group, 13 patients (65%) tolerated sublingual immunotherapy therapy very well, 6 (30%) good, 1 (5%) moderate. On the other hand, 11 asthmatic patients with allergic rhinitis (55%) tolerated therapy very well, 7 patients (35%) good, 2 patients (10%) moderate **(Table 15)**. These results were similar to that of **Al-Shehri, 2002**[26] who reported that from the 182 documented patients 125 (68.7 %) tolerated therapy very well, 50 (27.5 %) good, 4 (2.2 %) moderate and one patient (0.5 %) bad. Also, **Steiner** ***et al.,*** **2009** [31] reported that tolerability of SLIT were 85% rated "excellent" , 12% "good", 3% of patients reported moderate side effects but no patient rated "bad". The following score was offered for selection: 1. excellent, no side effects; 2. good, slight side effects; 3. moderate side effects; and 4. bad, not acceptable. Our results revealed that 13 out of 20 (65%) asthmatic patients group had reduction of symptoms, 7 out of 8 patients (87.5%) had reduction of nocturnal asthma, 7 out of 11 patients (63.63%) had reduction of asthmatic attacks and 14 out of 20 patients (70%) had reduction of need to rescue treatment one year after the course of sublingual immunotherapy **(Table16).** On the other hand, 15 out of 20 (75%) asthmatic patients with allergic rhinitis group had reduction of symptoms, 11 out of 12 patients (91.66%) had reduction of nocturnal asthma, 9 out of 12 patients (75%) had reduction of asthmatic attacks 15 out of 20 patients (75%) had reduction of need to rescue treatment, and 13 patients (65%) had reduction of nasal symptoms one year after the course of sublingual immunotherapy **(Table17).** These results were similar to that of **Bahceciler** ***et al.,*** **2005**[29] who have reported significantly reduced asthma symptoms and medication use, reduced number of asthma exacerbations, increased FEV1, and increased peak expiratory flow rate with SLIT. Similarly, **Tripathi** ***et al.,*** **2008**[28] who had reported that results of sublingual immunotherapy using multiple allergen showed significant reduction in symptoms, medication, and improvement in PEFR by modifying the natural history of the disease and preventing the onset of new sensitization. Also, **Abramson** ***et al.,*** **2003** [34] reported in a meta-analysis of allergen immunotherapy that included 75 prospective, randomised controlled trials of immunotherapy for asthma showed a reduction in the need for medication, a reduction in bronchial hyper-responsiveness, and improvement in forced expiratory volume in 1 second (FEV1). Another meta-analysis of SLIT efficacy in the treatment of adult and pediatric allergic rhinitis by **Wilson** ***et al.,*** **2005**[2] assessed 22 studies and found a statistically significant symptom reduction and a statistically significant reduction in medication use, supporting the efficacy of SLIT in allergic rhinitis. **Lue** ***et al.,*** **2006** [35] and **Bahceciler** ***et al.,***[36] have reported significantly reduced asthma symptoms and medication use, reduced number of asthma exacerbations, increased FEV1, and increased peak expiratory flow rate with SLIT. On The other hand, **Ferrés** ***et al.,*** **2010**[37] reported that as for the long-term effect of SLIT on asthma symptoms, they did not find any reduction in the consumption of treatments for asthma between baseline and the six month visit. Moreover, they did not find any temporal improvement in asthma severity, assessed using the GAS, or in respiratory function. The clinical condition of the patients selected in their study might explain the lack of a significant improvement in asthma severity: peak flow and FEV1 at baseline were markedly high, indicating that asthma was well controlled in these patients when they initiated the treatment with SLIT. **Wilson** ***et al.,*** **2006** [14] reported that in the patients who received SLIT, researchers observed a significant reduction of 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.

There are several limitations to our study. First, the relative small number of patients and limited follow up period of the study 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. So, studies on the efficacy of monotherapy vs polytherapy in SLIT treatment regimens are lacking.

Third, loss of follow up of patients after 28 months to evaluate long term outcome of SLIT in these patients.

Conclusion:

From this study we concluded that sublingual immunotherapy is a safe treatment which significantly reduces symptoms and medication requirements, 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.

Corresponding author
Zakia Abu-Zahab,
Department of Clinical Pathology, Faculty of Medicine For Girls, Al Azhar University, Egypt.
omima468@yahoo.com

5.References:

1. **Susan M., Harding M.D.:** Gastroesophageal reflux, Asthma and mechanism of interaction. Am. J. Med. **2001**; Dec 3 III Suppl 8A8S-12S.
2. **Wilson D.R., Torres M.L., Durham S.R.:** Sublingual immunotherapy for allergic rhinitis: systematic review and meta-analysis. Allergy. Volume 60 Page 4 - January 2005.
3. **Bousquet J., Van Cauwenberge P., Khaltaev N.**: Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol., 2001; 108: S147-334.
4. **Janet Rimmer and John W Ruhno :** Rhinitis and asthma: united airway disease. The Medical Journal of Australia MJA., 2006; 185 (10): 565-571.
5. **Cox L.S.:** Sublingual immunotherapy, part 1: Review of clinical efficacy -- Will this soon be an option for some of your patients?. J Respir Dis. 2007; 28(4):162-168.
6. **Ortolani C., Agostinis F., Amoroso S., Ariano R., Barbato A., Bassi M., Cadario G., Campi P., Cardinale F. et al:** Practice parameters for sublingual immunotherapy. Monaldi Arch Chest Dis. 2006 Mar;65(1):44-6.
7. **Casale T.B., Canonica G.W., Bousquet J., Cox L., Lockey R., Nelson H. S., Passalacqua G.:** Recommendations for appropriate sublingual immunotherapy clinical trials The Journal of Allergy and Clinical Immunology. Volume 124, Issue(4): Pages 665-670, October 2009.
8. **Radulovic S, Calderon MA, Wilson D, Durham S.:** Sublingual immunotherapy for allergic rhinitis (Review). Copyright © 2011 Issue 2. The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
9. **Crimi E., Milanses M., Oddera S.:** Inflammatory and mechanical factors of allergen- induced broncho-constriction in mild asthma and rhinitis. J Appl Physiol. 2001; 91:1029-34.
10. **Halpern M.T., Schmier J.K., Richner R.:** Allergic rhinitis: a potential cause of increased asthma medication use , costs and morbidity. J Asthma. 2004; 41: 117-26.
11. **Corren J.,Adinoff A.D., Buchmeier A.S.:** Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. J Allergy Clin Immunol. 1992; 90:250-6.
12. **Wood R.A.& Eggleston P.A.:** The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. Am J Respir Crit Care Med 1995; 151: 315-20.
13. **Crystal- Peters J., Neslusan C., Crown W.H. :** Treating allergic rhinitis in patients with combined asthma: The risk of asthma- related hospitalizations and emergency department visits. J Allergy Clin Immunol. 2002; 109:57-62.
14. **Wilson D.R., Torres L.M., Durham S.R.:** Sublingual immunotherapy for allergic rhinitis (Cochrane Review). The Cochrane Library, Issue 3, 2006. Chichester, UK: John Wiley & Sons, Ltd.
15. **Passalacqua G, Durham SR.:** Global Allergy and Asthma European Network. Allergic rhinitis and its impact on asthma update: allergen immunotherapy. J Allergy Clin Immunol. 2007; 119(4):881-91.
16. **Mohapatra SS, Qazi M, Hellermann G.**: Immunotherapy for allergies and asthma: present and future. Curr Opin Pharmacol. 2010; 10 (3): 276-88.
17. **Nelson HS.**: Allergen immunotherapy: where is it now? J Allergy Clin Immunol. 2007; 119(4):769-79.
18. **Senti G, Freiburghaus AU, Kundig TM.**: Epicutaneous/ transcutaneous allergen-specific immunotherapy: rationale and clinical trials. Curr Opin Allergy Clin Immunol. Curr Opin Allergy Clin Immunol. 2010; 10(6): 582-6.
19. **Nouri-Aria KT, Wachholz PA, Francis JN, Jacobson MR, Walker SM, Wilcock LK , *et al.***: Grass pollen immunotherapy induces mucosal and peripheral IL-10 responses and blocking IgG activity. J Immunol. 2004; 172 (5): 3252-9.
20. **Larché M, Akdis CA, Valenta R.:** Immunological mechanisms of allergen-specific immunotherapy. Nat Rev Immunol. 2006; 6(10):761-71.
21. **Passalacqua G., Lombardi C., Canonica G.W.:** Sublingual immunotherapy: an update. Curr Opin Allergy Clin Immunol. 2004 Feb; 4(1): 31-6.
22. **Storms W.W., Bodman F. S., Nathan A. R. and Byer P.:** Nocturnal Asthma Symptoms May Be More Prevalent than We Think. Journal of Asthma. 1994, Vol. 31, No.(4): , Pages 313-318.

23. **Kim ST, Han DH, Moon IJ, Lee CH, Min YG, Rhee CS.:** Clinical and immunologic effects of sublingual immunotherapy on patients with allergic rhinitis to house-dust mites: 1-year follow-up results. Am J Rhinol Allergy. 2010 Jul-Aug;24(4):271-5.
24. **La Grutta S**., **Arena A**., **D'Anneo W.R**., **Gammeri E**., **Leonardi S**., **Trimarchi A**., **Platania D**., **La Rosa M**.: Evaluation of the antiinflammatory and clinical effects of sublingual immunotherapy with carbamylated allergoid in allergic asthma with or without rhinitis. A 12-month perspective randomized, controlled, trial. Allerg Immunol (Paris). 2007 Feb; 39(2):40-4.
25. **Abd Elwadowd M. R., and Salem K.A.:** Sublingual immunotherpay as a relevant alterative in treatment of allergic rhinitis, an intervention study. Egypt. J. Med. Lab. Sci., (ESIC) 2005, Vol. 14, No.(1):31-38.
26. **Al-Shehri A.M.**: Specific Sublingual Immunotherapy. The Internet Journal of Asthma, Allergy and Immunology. 2002. Volume 2 Number(2): DOI: 10.5580/c60.
27. **Wise S. K., Woody J., Koepp S., Schlosser R. J.:** Quality of life outcomes with sublingual immunotherapy. American Journal of Otolaryngology - Head and Neck Medicine and Surgery, 30 (2009) :305-311.
28. **Tripathi D.M., Joshi S.V., Dhar H.L.:** Efficacy of Sublingual Immunotherapy with Multiple Allergens in Bronchial Asthma. Bombay Hospital Journal, Vol. 50, No.(2):…227-231. 2008.
29. **Bahceciler N.N., Arikan C., Taylor A., Akdis M., Blaser K., Barlan I.B., Akdis C.A.:** Impact of Sublingual Immunotherapy on Specific Antibody Levels in Asthmatic Children Allergic to House Dust Mites. Vol. 136, No. (3):… 287-294 .., 2005.
30. **Calamita Z., Saconato H., Pel A.B., Atallah N.:** Efficacy of sublingual immunotherapy in asthma: systematic review of randomized-clinical trials using the Cochrane Collaboration method. Allergy, 2006: 61: 1162-1172.
31. **Pajno G.B., Vita D.,Caminiti L.:** Children compliance with allergen immunotherapy according to administration routes**.** J Allergol Clin Immunol. 2005; 116:1380-1381.
32. **Steiner L., Engel T., Nöding A., Licht M., Delaney A., Distler A., Zwacka G. and Markert U.R.:** Description of Long Term Outcome of Sublingual Immunotherapy Treatment in Children: A Follow-Up Observation Through Phone Interviews. The Open Allergy Journal, 2009, 2:30-37.
33. **Girado G.B., Marcucci F., Sensi L.:** The safety of sublingual swallow immunotherapy: an analysis of published studies. Clin Exp Allergy. 2005; 35: 565- 571.
34. **Abramson MJ, Puy RM, Weiner JM.:** Allergen immunotherapy for asthma. Cochrane Database Syst Rev 2003; (4): CD001186.
35. Lue K, Lin Y, Sun H, *et al.* Clinical and immunologic effects of sublingual immunotherapy in asthmatic children sensitized to mites: a double-blind, randomized, placebo-controlled study. Pediatr Allergy Immunol., 2006; 17: 408-15.
36. Bahceciler N, Isik U, Barlan I, et al. Efficacy of sublingual immunotherapy in children with asthma and rhinitis: a double-blind, placebo-controlled study. Pediatr Pulmon, 2001;32:49-55.
37. **Ferrés J., Justicia J.L., García M.P., Mu˜noz-Tudurí M., Alv V.:** Efficacy of high-dose sublingual immunotherapy in children allergic to house dust mites in real-life clinical practice. Allergol Immunopathol (Madr). 2010. doi:10.1016/j. aller. 2010.01.008.

6/12/2012