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ORIGINAL ARTICLE

Efficacy of Sublingual Immunotherapy (SLIT) in the Management of Mite Sensitive Bronchial Asthma with Allergic Rhinitis

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Abstract

Background: *Sublingual immunotherapy (SLIT) has been recommended as a viable alternative to subcutaneous injection therapy in the treatment of airway allergies, though more data is needed from well controlled studies documenting its efficacy in different ethnic population.*

Objective: *To find out an ideal treatment of bronchial asthma with allergic rhinitis and to find out whether immunotherapy in asthma and allergic rhinitis improve control.*

Material & Methods: *This double blind placebo controlled study (DBPC) was carried out in Department of Respiratory Medicine of National Institute of Diseases of the Chest & Hospital (NIDCH), Dhaka, during the period of March 2009 to February 2010. In this study, the efficacy and safety of SLIT with D. pterosynsinus and D.farinae extracts as compared with those of placebo therapy in patients with moderate persistent bronchial asthma with allergic rhinitis was assessed. Sixty-four patients aged 15-55 years were double-blinded and randomly assigned to either SLIT or placebo. Patients and investigators made evaluation of treatment effectiveness at 4 weekly interval during treatment as well as follow-up phase. Control of asthma was assessed by asthma control test and asthma quality of life score was assessed by Juniper AQLQ at 4 weekly interval for 24 weeks and 8 weekly interval for two times.*

Results: *A total number of 32 patients were observed by giving SLIT and 29 were treated with placebo. 3 (9.3%) patients for placebo groups were dropped out due to lack of efficacy. There were predominance of female (68.8%) in SLIT group and majorities were in the age group of 20-40 years (68.8%) with mean age 26.59±8.62 in SLIT group and 27.28±10.53 in placebo group. The symptomatic improvement of bronchial asthma score after giving SLIT and placebo is increasing gradually for 4^{th} (20.09±3.69 vs 20.93±3.82) to 8^{th}*

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(21.09±2.57 vs 18.90±3.02) follow-up which became statistically significant (P<0.001). The experimental Event Rate (EER) is 28.1%, the Control Event Rate (CER) is 41.4%, the Relative Risk Reduction (RRR) is 32.1%, the Absolute Risk Reduction (ARR) is 13.3%, the Number Needed to Treat (NNT) is 7.5. The symptomatic improvements of allergic rhinitis, after giving treatment with SLIT is gradually becoming statistically significant (p<0.5). The duration of sneezing, rhinorrhoea, nasal blockage, itching of nose is improving from 1st to 8th follow-up, i.e after 32 weeks (p<0.05). The control Event Rate (CER) is 55.2%. The Experimental Event Rate (EER) is 28.1%. The Relative Risk Reduction (RRR) is 49.1%. The Absolute Risk Reduction (ARR) is 27.1%. The Number Needed to Treat (NNT) is 3.4. The improvements of symptoms in the last 4 weeks is noticed which was more completely controlled in SLIT group (12.5%) than placebo (10.3%) group in 1st follow-up and became statistically significant in 6th to 8th follow-up.

Conclusion: *Our result indicated that 40 weeks SLIT is of clinical benefit to patients who are mite sensitive moderate persistent asthma with rhinitis in Bangladesh.*

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Introduction:

Asthma is a multifactorial and complex chronic disease characterized by variable airflow obstruction and airway hyper responsiveness[1]. Allergic rhinitis is also a global health issue with a considerable socio-economic impact, seriously affecting human productivity and quality of life. Epidemiological studies have shown that 80% of asthmatics have co-existent rhinitis. Its prevalence is known to be increasing, particularly among children. Interactions between hereditary and changing environmental factors may be responsible for the increased prevalence of asthma[2].

Allergen mostly the *mite, food* and *animal* allergen are the main contributory factor for both the diseases. The most common allergens are house dust mite, animal dander, pollens, moulds & food stuffs[3]. Patients with asthma tend to have an increase in airway reactivity to other variety such stimuli, such as exercise, cold air, and viruses[1]. Most patients with asthma have an allergic component to their disease. Allergic food and animal can easily be avoided but mite can't be, as it is ubiquitous. So it is wise to immunize against mite allergen in mite allergen positive patient along with avoidance of allergic foods and contact with animals to prevent bronchial asthma and allergic rhinitis.

The reaction to inhalant allergens can only be achieved with appropriate allergen avoidance measures and specific immunotherapy, which is believed to be the only treatment method that can change the natural history of the disease[4]. In this respect subcutaneous immunotherapy has been widely applied and has been shown to be effective in reducing symptoms[5]. Uncommon with severe and nearly fatal systemic reactions have begun to worry physicians[6] and repeated injections have led to serious complaints especially among children[7]. Thus, alternative routes of immunotherapy have been proposed. Among them, sublingual immunotherapy (SLIT), by which oral tolerance is induced at mucosal surfaces, has been gaining the confidence of practitioners because of its good safety profile and its effectiveness in the context of allergic airway disease[8].

Specific allergen immunotherapy (SIT) involves the administration of allergen extracts to modify or abolish symptoms associated with atopic allergy[9]. The traditional subcutaneous route is burdened with the severe adverse reactions[3]. In this study an attempt has been made to administer the allergen specific vaccine through oral route using

mite allergen in allergic bronchial asthma and allergic rhinitis. SLIT has been used in Europe, Asia and Australia for the treatment of allergic respiratory diseases and is now considered an efficacious and safe alternative to SCIT (subcutaneous immunotherapy)[10].

The basis of sublingual immunotherapy is treatment of the underlying allergic sensitivity. Allergic symptoms improve as the allergic sensitivity improved. As a safe and effective method of treating the underlying disease, sublingual immunotherapy is capable of modifying the natural progression of allergic disease which can begin with allergic food sensitivities & eczema in young children and progress though allergic rhinitis and asthma in older children & adults[11].

In a number of double-blind, placebo-controlled studies sublingually-administered allergenic extracts have been demonstrated to be an effective therapeutic modality in respiratory allergic disease[12]. Their level of tolerance has also been confirmed in pharmaco vigilance studies both in adults and in children[13]. Furthermore, among all the alternatives that have been investigated to the subcutaneous administration of allergenic hyposensitizing therapy with the purpose of increasing the safety and comfort of administration to the allergic patient, the sublingual route has been shown to be the clinically most effective one[12]. SLIT offers some logistic advantages and seems to be safe during allergen by mouth rather than by injection should decrease the cost of immunotherapy[14]. Sublingual immunotherapy, or SLIT, has a very good safety profile and is given at home in adults and children[12].

Although several reports are available on SLIT in European, American and some Asian populations, these may not be applicable for the Bangladeshi population. Therefore the current study has been undertaken in Bangladeshi subjects. So the objective of this present study was to immunize sublingually against mite who were mite allergen positive patients suffering from asthma with allergic rhinitis, along with avoidance of allergic foods and contact with animals for the Bangladeshi population, for the first time to observe its efficacy in our population.

Hypothesis

Sublingual immunotherapy (SLIT) of mite extract will reduce severity & frequency of attack of asthma and allergic rhinitis and improve symptoms.

Objective:

General Objectives: To find out an ideal treatment of bronchial asthma with allergic rhinitis.

Specific Objectives: To find out whether immunotherapy treatment in asthma with allergic rhinitis improve control.

Methodology:

This was a double blind randomized placebo controlled trial (RCT) study. This was carried out in the department of Respiratory Medicine of National Institute of diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka during the period from March 2009 to February 2010.

The patients groups were recruited from renowned chest physicians' clinic in Dhaka city and also from the out patient (OPD) and inpatient department of National Institute of Diseases of the Chest and Hospital (NIDCH), Mohakhali, Dhaka.

A total of 64 patients were enrolled in this study and they were divided into two groups. Each group contained 32 patients (32 cases and 32 controls). All were suffering from bronchial asthma with allergic rhinitis.

The sampling technique was consecutive random sampling as per inclusions and exclusion criteria.

Inclusion criteria

- Age: In between 15- 55 years.
- Patients with both sexes
- Non smoker
- Bronchial asthma diagnosed as per ATS criteria
- Allergic rhinitis diagnosed as per ARIA criteria
- Mite allergen positive patients ie. skin prick test positive (wheal>5mm2 in area) to standardized extract of Dermatophagoides pterosynsinus (D.pt) and Dermatophagoides farinae (D.f)
- Participants, who gave consent and willing to comply with the study procedure, were included.

Exclusion criteria

- Age: under 15 years and above 55 years
- Smokers
- Had a disease causing asthma like symptoms, e.g.
  - ABPA

- Tropical pulmonary eosinophilia
- Loeffler' syndrome
- Polyarteritis nodosa

- Immunocompromised patient like
  - pulmonary tuberculosis
  - Diabetes mellitus
- Pregnancy
- Severely ill patients
- Patients or attendants unwilling to take part in the study

Study Procedure

This was a randomized, placebo-controlled, double-blind study with 40-weeks treatment phase to determine the role of sublingual immunotherapy in patients of moderate persistent bronchial asthma with allergic rhinitis. Patients were recruited from National Asthma Centre (NAC) of National Institute of Diseases of chest & Hospital (NIDCH), Mohakhali, Dhaka and from renowned chest physicians clinic in Dhaka city.

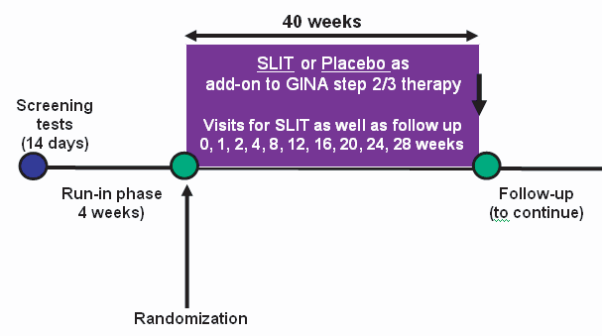
The study was comprised of four phases,

i. 14-days screening period for evaluating eligibility
ii. 4-weeks run-in phase
iii. then 40- weeks drug add-on treatment phase as well as
iv. follow-up phase

Patients came for a study visits at screening, and every 2 week during the run-in phase. Patients aged 15-55 years with moderate persistent asthma (GINA step2/3) along with allergic rhinitis were enrolled in the study.

During the first week of the run-in period, each subject's asthma management were reviewed to assess mite allergen sensitivity, inhaler technique etc. Asthma medication was adjusted to achieve the best control. The doses of Inhaled corticosteroids and Long Acting Beta Agonists (taken separately or as a ûxed combination) and other concomitant asthma medications were kept constant during the last 2 weeks of the run-in period and were maintained during the treatment and follow up period. Patients were permitted short-acting β_2-agonist rescue medication as required. To minimize a potential treatment group imbalance of clinical asthma management practice and concomitant asthma medication use, randomization and stratified for receiving immunotherapy and placebo. Investigators and personnel involved in monitoring the study were remained blinded throughout the study periods.

Medications were provided to the patient and were asked to take on routinely as per allergen doses schedule & were asked to come at 4 weekly intervals for 28 weeks for treatment as well as follow up. Patients and investigators made evaluations of treatment effectiveness at 4 weekly intervals during treatment phase and follow up phase. Qualities of Life were assessed by questionnaire of Asthma Control Test (ACT) and also with the help of Juniper Adult Asthma Quality of Life Questionnaire (AQLQ)[15] at weekly intervals for 28 weeks and 8 weekly intervals to continue. All visits were included the assessment of vital signs and physical examination.



Results and Observation:

A total number of 32 patients were observed by giving the SLIT and 29 were treated with placebo. Among 32 patients treated with SLIT female was predominant than male which was 22 (68.8%) and 10 (31.3%) patients respectively. In case of 29 placebo group male was predominant than female which was 16 (55.2%) and 13 (44.8%) respectively. The difference between male and female was not significant (p=0.059).

Table-I

Distribution of Study population according to age by groups

Age (in year)	Group		p value*
	SLIT	Placebo	
<20	9 (28.1)#	9 (31.0)	
20-40	22 (68.8)	16 (55.2)	
>40	1 (3.1)	4 (13.8)	
Total	32(100.0)	29(100.0)	
Mean ± SD	26.59 ± 8.62	27.28 ± 10.53	0.719

*t test was done to measure the level of significance. #Figure within parentheses indicates in percentage.

Table I shows the distribution of study population according to age by groups. The difference between SLIT and Placebo group is not significant (p=0.719).

Table-II

Distribution types of Symptoms of asthma by groups

Types of Symptoms	Group		p value*
	SLIT	Placebo	
Breathlessness	28 (87.5)#	26 (89.7)	0.792
Wheeze	25 (78.1)	25 (86.2)	0.412
Chest tightness	27 (84.4)	24 (82.8)	0.865
Cough	30 (93.8)	24 (82.8)	0.179

*Chi square test was done to measure the level of significance. #Figure within parentheses indicates in percentage.

Table II shows the distribution types of symptoms of asthma by groups. All of these are not statistically significant (p<0.05).

Table-III

Distribution of symptoms of allergic rhinitis by groups

Symptoms	Group		p value*
	SLIT	Placebo	
Sneezing	30 (93.8)	29 (100.0)	0.171
Runny nose	29 (90.6)	25 (86.2)	0.589
Nasal blockage	28 (87.5)	27 (93.1)	0.463
Nasal itching	27 (84.4)	24 (82.8)	0.865
Symptoms of conjunctivitis	26 (81.3)	19 (65.5)	0.163

*Chi square test was done to measure the level of significance

Table III shows the distribution of symptoms of allergic rhinitis by groups. The differences in symptoms of allergic rhinitis between SLIT and placebo group are not significant (p>0.05).

Table IV

Distribution of follow up of Bronchial asthma by Asthma Control Test.

Follow up for Bronchial asthma	Group		p value*
	SLIT	Placebo	
Follow up 1	21.22 ± 3.14	21.52 ± 2.96	0.705
Follow up 2	22.03 ± 2.44	21.72 ± 2.52	0.631
Follow up 3	22.03 ± 2.18	21.59 ± 2.95	0.509
Follow up 4	20.09 ± 3.69	20.93 ± 3.82	0.388
Follow up 5	21.09 ± 2.57	18.90 ± 2.94	0.003
Follow up 6	21.28 ± 2.30	18.66 ± 3.06	0.001
Follow up 7	21.38 ± 2.30	18.72 ± 2.98	0.001
Follow up 8	21.53 ± 2.57	18.90 ± 3.02	0.001

*t test was done to measure the level of significance.
Data was shown as Mean ± SD.

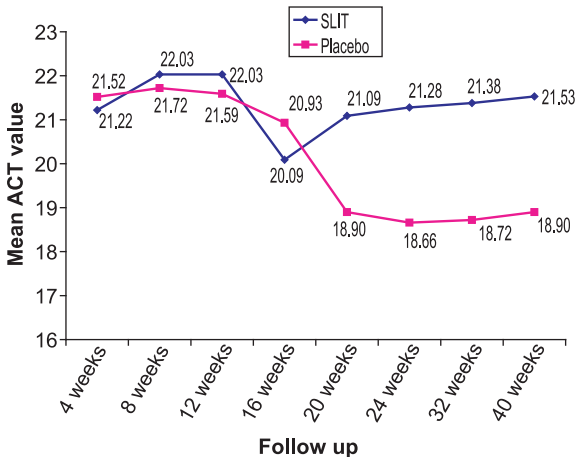


Fig.-1: *Line diagram showing distribution of follow up of both groups of patients by Asthma Control Test (ACT) clearly denoting improvements in SLIT group .Statistically significant result between two groups is noted from 24 weeks onward.*

Table-V

Distribution of total Bronchial asthma score by Asthma Control Test (ACT) in final follow up

Bronchial asthma Total score		Group	
		SLIT	Placebo
<20 (not controlled)	9 (28.1)	12 (41.4)	21 (34.4)
20-24 (somewhat controlled)	18 (56.3)	17 (58.6)	35 (57.4)
25(well controlled)	5 (15.6)	0 (.0)	5 (8.2)
Total	32 (100.0)	29 (100.0)	61 (100.0)

Control Event Rate (CER) = 41.4%, Experimental Event Rate (EER) = 28.1%
Relative Risk Reduction (RRR) = (1-EER/CER) = (CER-EER)/CER = 32.1%
Absolute Risk Reduction (ARR) = CER-EER = 13.3%
Number Needed to Treat (NNT) = 7.5

Table IV shows the distribution of follow up of bronchial asthma by groups. The 1st follow up in SLIT and placebo group is 21.22 ± 3.14 and 21.52 ± 2.96 respectively. This is not statistically significant (p=0.705). Similar is the situation in 2nd, 3rd and 4th follow up. The 5th follow up in SLIT and placebo group is 21.09 ± 2.57 and 18.90 ± 2.94 respectively. This is statistically significant (p= 0.003). Statistically significant differences are also noted between the two groups in 6th, 7th and 8th follow up (p= 0.001).

Table-VI

Distribution of follow up of Bronchial Asthma at 1st follow up by groups

Asthma Quality of Life Score	Group		p value*
	SLIT	Placebo	
Symptoms			
Dyspnoea due to asthma	5.59 ± 1.48	6.00 ± 1.16	0.241
Feel bothered by coughing	6.06 ± 0.98	5.72 ± 1.41	0.287
Experience chest tightness	5.94 ± 1.22	5.90 ± 1.50	0.907
Sleep disturbance at night	6.38 ± 0.83	6.31 ± 1.07	0.792
Experience a Wheeze	6.50 ± 0.84	6.41 ± 0.95	0.708
Environmental pollutant			
Feel bothered to avoid dust	5.06 ± 1.68	5.21 ± 1.11	0.692
Feel bothered to avoid cigarette	5.34 ± 1.70	5.52 ± 1.24	0.653
Feel bothered due to air pollution	5.19 ± 1.67	5.69 ± 1.31	0.201
Emotions			
Feel frustrated due to asthma	5.69 ± 1.38	6.28 ± 1.07	0.069
Feel afraid of lacking medication	5.97 ± 1.36	6.34 ± 0.67	0.170
Feel concerned due to asthma	5.44 ± 1.61	5.52 ± 1.38	0.837
Activities			
Strenuous activities	5.22 ± 1.34	5.52 ± 0.91	0.309
Moderate activities	5.78 ± 1.13	6.17 ± 0.85	0.129
Social activities	6.13 ± 1.07	6.41 ± 0.95	0.271
Work-related activities	6.16 ± 1.14	6.66 ± 0.81	0.052

*t test was done to measure the level of significance
Data was shown as Mean ± SD.

Table VII

Distribution of follow up of Bronchial Asthma at 8th follow up by groups

Asthma Quality of Life Score	Group		p value*
	SLIT	Placebo	
Symptoms			
Dyspnoea due to asthma	5.88 ± 0.91	4.59 ± 0.87	0.001
Feel bothered by coughing	5.72 ± 0.81	4.79 ± 0.82	0.001
Experience chest tightness	6.03 ± 1.00	4.10 ± 1.24	0.001
Sleep disturbance at night	6.16 ± 0.85	5.38 ± 0.86	0.001
Experience a Wheeze	6.16 ± 1.08	5.03 ± 1.18	0.001
Environmental			
Feel bothered to avoid dust	5.34 ± 0.83	4.62 ± 0.90	0.002
Feel bothered to avoid cigarette	5.22 ± 0.71	4.62 ± 0.90	0.006
Feel bothered due to air pollution	5.13 ± 0.98	4.59 ± 0.98	0.036
Emotions			
Feel frustrated due to asthma	5.78 ± 0.87	5.28 ± 0.88	0.028
Feel afraid of lacking medication	5.94 ± 0.88	4.76 ± 0.99	0.001
Feel concerned due to asthma	5.09 ± 1.55	5.31 ± 1.14	0.540
Activities			
Strenuous activities	5.47 ± 1.16	5.03 ± 0.73	0.084
Moderate activities	6.13 ± 1.10	4.86 ± 0.95	0.001
Social activities	6.16 ± 1.08	4.79 ± 0.94	0.001
Work-related activities	6.09 ± 1.06	5.17 ± 0.89	0.001

*t test was done to measure the level of significance.
Data was shown as Mean ± SD.

Table VIII

Distribution of cases according to the duration of allergic symptoms (sneezing/ rhinorrhoea/nasal blockage/itching of nose)

	Group		p value*
	SLIT	Placebo	
1st follow up			
Intermittent	20 (62.5)#	21 (72.4)	0.616
Persistent	6 (18.8)	5 (17.2)	
Not at all	6 (18.8)	3 (10.3)	
2nd follow up			
Intermittent	15 (46.9)	19 (65.5)	0.293
Persistent	10 (31.3)	7 (24.1)	
Not at all	7 (21.9)	3 (10.3)	
3rd follow up			
Intermittent	23 (71.9)	22 (75.9)	0.413
Persistent	5 (15.6)	6 (20.7)	
Not at all	4 (12.5)	1 (3.4)	
4th follow up			
Intermittent	19 (59.4)	20 (69.0)	0.419
Persistent	9 (28.1)	8 (27.6)	
Not at all	4 (12.5)	1 (3.4)	
5th follow up			
Intermittent	21 (65.6)	21 (72.4)	0.742
Persistent	7 (21.9)	6 (20.7)	
Not at all	4 (12.5)	2 (6.9)	
6th follow up			
Intermittent	12 (37.5)	8 (27.6)	0.163
Persistent	9 (28.1)	15 (51.7)	
Not at all	11 (34.4)	6 (20.7)	
7th follow up			
Intermittent	12 (37.5)	8 (27.6)	0.041
Persistent	9 (28.1)	17 (58.6)	
Not at all	11 (34.4)	4 (13.8)	
8th follow up			
Intermittent	11 (34.4)	9 (31.0)	0.049
Persistent	9 (28.1)	16 (55.2)	
Not at all	12 (37.5)	4 (13.8)	

*Chi-square test was done to measure the level of significance. #Figure within parentheses indicates in percentage.
CER = 55.2%, EER = 28.1%, RRR = 49.1%. ARR = 27.1%, NNT = 3.4

Table V shows the distribution of total bronchial asthma score by Asthma Control Test (ACT) in final follow up, by which NNT is calculated.

Table VI shows the distribution of follow up of bronchial asthma at 1st follow up by groups. The differences in symptoms of asthma, feelings due to environmental pollutants, emotions and activities are not statistically significant (p>0.05).

Table VII: Distribution of follow up of bronchial asthma at 8th follow up by groups. In SLIT and placebo group Asthma Quality of Life Score of symptoms, feelings due to environmental pollutions, emotions and activities are statistically significant(p=0.001) between the two groups.

Table VIII shows the distribution of cases according to the duration of sneezing/ rhinorrhoea/ nasal blockage / itching of nose...Statistically significant differences between the two groups are noted during 7th follow up and 8th follow up (p<0.05). NNT is 3.4.

Discussion:

The therapeutic use of sublingually administered allergenic extract is progressively increasing. To this increase the considerable number of double blind studies confirming the efficacy and safety of this route of administration has doubtlessly contributed.

In contraposition to the subcutaneous route, with which the patient must go to the specialist's clinic or at least to health care centre for administration of the treatment doses, in the case of sublingual one the patient administer himself the treatment dose at his own house. Because of this and also because this is a rather protracted therapy, it is unavoidable to establish mechanisms allowing the specialist, in the usual conditions of his everyday clinical practice, to assess not only the efficacy and safety of the therapy but also the patient is adequately complying with it. Only in this way the desired therapeutic success is achieved.

In this double blind placebo controlled study, we assessed the efficacy and safety of SLIT with D.pterosynsinus & D.farinae extracts as compared with those of placebo therapy in patients of moderate bronchial asthma with allergic rhinitis.

A total number of 32 patients were observed by giving the SLIT and 29 were treated with placebo as add on to GINA (Global Initiative to Asthma) step 2 or 3 therapy. Among 32 patients treated with SLIT female was predominant than male which was 22(68.8%) and 10(31.3%) patients respectively. In case of 29 placebo group male was predominant than female which was 16(55.2%) and

13(44.8%) respectively. The difference between male and female was not significant (p=0.059). Asthma is a common chronic pulmonary disease whose prevalence varies greatly with the sex and age of the patient. This result is consistent with a number of studies and reported that asthma is more prevalent in female than male[16]. A similar study conducted on a Kuwaiti population also reported that sex was an independent predictor of asthma in individuals[17].

One feature of this study is, 3 out of 32 (9.3%) patients from placebo groups, dropped out, which decreased the power of the analysis. However, it should be stressed that patients drop out because of lack of efficacy in the placebo group indicates a trend towards better compliance in the active treatment group due to efficacy of immunotherapy. In one DBPC study of 72 sample size of 24 months duration , stated that the number of patients dropped out in placebo group was 15 out of 38 (39.5%)[18], which was much higher in comparison to our study, although the duration of that study was 24 months where as our study was 12 months.

The distribution of follow up of bronchial asthma by groups by Asthma Control Test is observed. The 1st follow up in SLIT and placebo group is 21.22 ± 3.14 and 21.52 ± 2.96 respectively. This is not statistically significant (p=0.705). The 2nd follow up in SLIT and placebo group is 22.03 ± 2.44 and 21.72 ± 2.52 respectively. This is not statistically significant (p= 0.631). The 3rd follow up in SLIT and placebo group is 22.03 ± 2.18 and 21.59 ± 2.95 respectively. This is not statistically significant (p= 0.509). The 4th follow up in SLIT and placebo group is 20.09 ± 3.69 and 20.93 ± 3.82 respectively. This is not statistically significant (p= 0.388). The 5th follow up in SLIT and placebo group is 21.09 ± 2.57 and 18.90 ± 2.94 respectively. This is statistically significant (p= 0.003). The 6th follow up in SLIT and placebo group is 21.28 ± 2.30 and 18.66 ± 3.06 respectively. This is statistically significant (p= 0.001). The 7th follow up in SLIT and placebo group is 21.38 ± 2.30 and 18.72 ± 2.98 respectively. This is also statistically significant (p= 0.001). The 8th follow up in SLIT and placebo group is 21.53 ± 2.57 and 18.90 ± 3.02 respectively. This is also statistically significant (p= 0.001).

Data indicates that initiation of SLIT in this study has shown statistically significant symptom reduction in a small cohort from baseline to the maintenance phase of therapy.

As many SLIT protocol exists worldwide timing of expected symptom improvement with SLIT is difficult to predict. It may vary from as early as 2 months to as late as 5 years[19].

Improvement of symptom was noted as early as 28-32 weeks that is 7-8 months after initiating SLIT, during maintenance phase which is very much encouraging.

The asthma control test (ACT) score in final follow up was assessed. Among 32 patients of SLIT group bronchial asthma (ACT) score of 20-24 is 18 (56.3) cases followed by less than 20 score and 25 scores are 9 (28.1) cases and 5 (15.6) cases respectively. In 29 patients of placebo group ACT score 20-24 is 18 (56.3) cases followed by less than 20 score and 25 score which are 9 (28.1) cases and 5 (15.6) cases respectively. The Control Event Rate (CER) is 41.4%. The experimental Event Rate (EER) is 28.1%. The Relative Risk Reduction (RRR) is 32.1%. The Absolute Risk Reduction (ARR) is 13.3%. The Number Needed to Treat (NNT) is 7.5, which means if we treat 7.5 patients, one patient will be definitely benefited. This result is statistically significant.

SLIT takes at least 2 years of treatment before subjects see improvement in symptoms. Other studies show improvement within a single year of therapy. Less time is required to achieve a therapeutic effect with SLIT, since benefit can be observed within 3-4 months[20].

The improvement of this study is seen after 6th follow up that is after 6 months, which support Creticos[20]. The variation in effectiveness had been attributed to the differences in the dose of allergen used for the various studies. A meta-analysis in asthma was done by Bousquet , which included 25 trials and involving more than 1,000 adults and children. This meta-analysis demonstrated a significant effect of SLIT for most of the considered outcomes like symptoms, medications, pulmonary function, overall improvement, with the exception of asthma symptoms alone[21].

In another study which reported that SLIT significantly improved asthma symptom scores, reduced nasal symptoms and the use of rescue medications, improved forced expiratory volume

in 1 second[22]. In Taiwan a study indicated that 24 weeks SLIT is of clinical benefit to mite sensitive asthmatic and rhinitis patients of Taiwan[23]. Our study is very much consistent with this.

Most patients (84%) felt better or much better at the end of one year of treatment. Statistically significant difference was observed in asthmatic symptoms as well as nasal & ocular symptoms[12].

The clinical benefits and observation become more significant when considering patients with perennial mite allergy, a minimum follow-up period of 6 months is required[24]. Our study clearly shows this observation.

In the present study, we also noted that immunotherapy with house dust mite allergen given sublingually has improved symptoms in active treatment group than that of placebo in allergic rhinitis patient. The distribution of symptom like sneezing, rhinorrhoea, nasal blockage and itching of nose were assessed according to ARIA criteria[25], which shows intermittent – symptoms less than 4 days a week and persistent i.e. more than 4 days in a week. At the initiation of therapy in the 1st follow-up , after 4 weeks shows that Intermittent duration of SLIT and placebo groups are 20 (62.5%) and placebo 21 (72.4%) respectively. And the persistent symptoms are 6 (18.8%) and 5 (17.2%) respectively. This result is not statistically significant (P>0.05). No statistically significant result noted until up to 7th follow-up i.e. after 32 weeks.

At 32 weeks of follow-up the persistent duration in SLIT and placebo groups are 9 (28.1%) and 17 (58.6%) cases respectively (p<0.05). The intermittent duration of the symptoms are in 12 (37.5%) and 8 (27.6%) cases in SLIT and placebo groups respectively. No symptoms are seen in 11 (34.4%) and 4 (13.8%) cases in SLIT and placebo groups respectively. In 8th follow-up the intermittent duration in SLIT and placebo groups are 11 (34.4%) and 16 (55.2%) cases respectively (p<0.05). The persistent of the symptoms are in 9 (28.1%) and 15 (51.7%) cases in SLIT and placebo groups respectively. No symptoms are seen in 11 (34.4%) and 6 (20.7%) cases in SLIT and placebo groups respectively. This is statistically significant (P<0.05).

The control Event Rate (CER) is 55.2%. The Experimental Event Rate (EER) is 28.1%. The Relative Risk Reduction (RRR) is 49.1%. The Absolute Risk Reduction (ARR) is 27.1%. The Number Needed to Treat (NNT) is 3.4. It means, if we treat 3.4 patients, 1 patient will definitely be benefited, which is statistically significant. A meta-analysis which was done by Penagos also performed for asthma in pediatric patients and found a significant effect of SLIT on both asthma and rhinitis symptoms and rescue medication usage[26].

Another study enrolled 50 children with allergic rhinitis and asthma due to house dust mite in a placebo controlled manner. The investigator used SLIT for 6 months and found a significant improvement in the daily asthma score in therapy group in comparison to placebo group[27]. Our study also showed similar results.

Most SLIT studies have used single allergen monotherapy to evaluate efficacy where as a few studies have included more than one allergen in the treatment regimen[28]. In our study we have used single allergen monotherapy to evaluate.

The safety of SLIT has been one of its consistently highlighted features. Although some trials report fairly high rates of mild adverse events with SLIT, these reactions are typically limited to oral cavity pruritus, rhinitis, dry throat, throat irritation, nausea and other gastro-intestinal complaints. Commonly severe systematic reaction and life threatening adverse events are noted to be absent in SLIT trials. Withdrawal from SLIT trials because of adverse events is rare but withdrawal has been documented for blistering or burning of the oral cavity, severe oral cavity pruritus, vomiting and diarrhoea, abdominal pain, lingual oedema[29].

No serious adverse events are noted in our study other than minor oral discomfort and throat irritation. This happened to only 2 cases during maintenance phase. These adverse reactions remitted spontaneously and did not require any modification of dosage and schedule.

In the present study it is seen that adequate compliance with follow-up is achieved in almost all the patients and is correlated well with having a favorable opinion about the therapy.

Although these results are encouraging the results

should be interpreted with caution. In addition, symptom reduction is an important measure in an overall immunotherapy treatment paradigm; this study is limited to subjective ratings of symptom score only.

As many SLIT protocol exists, timing of expected symptom improvement is difficult to predict. We have noted symptom improvement as early as 24 weeks after initiating SLIT. Typical escalation period with SCIT are months length with mild slower increases in antigen dosing.

Finally medication use and immunological parameters were not assessed in this study and are also important measure to consider.

So our results indicated that 40 weeks SLIT is of clinical benefit to mite sensitive asthmatic and rhinitis patients in Bangladesh and there were no serious adverse events reported with initiation of SLIT in our study.

Conclusion:

In conclusion, the findings of this study permit to conclude that SLIT against house dust mite is statistically more significant in asthma and allergic rhinitis patients than placebo. The improvement of the symptoms of allergic rhinitis and asthma was not earlier than 28 weeks (6-7 months).

Although further work is needed to evaluate SLIT, the present study demonstrated the good safety profile and efficacy of the route of administration.

So our study suggests that immunotherapy results in clinical improvement of patients of asthma and rhinitis who are mite allergen positive and should be suggested in the management.

Recommendation:

For further study, the following recommendations are proposed:

- Additional randomized controlled trial with larger sample sizes and longer follow-up are necessary to support the growing body of evidence that SLIT is viable option for treatment of allergic patients in Bangladesh.
- Specific immunotherapy may be the cornerstone in the management of respiratory allergy since it is allergen specific, immune modulating and modifies disease progress. So, anti-mite SLIT may be added as add on therapy in moderate persistent asthma with allergic rhinitis cases.

References:

1. Borish L, Chipps B, Deniz Y, Gujrathi S, Zheng B, Dolan CM, for the TENOR Study Group. Total serum IgE levels in a large cohort of patients with severe or difficult-to-treat asthma. Ann Allergy Asthma Immunol; 2005; 95: 247-253
2. Pawankar R. Allergic rhinitis - a handbook for doctors. Bangladesh Society of Allergy & Immunology; 2004; 1: 11-12
3. Tripathi DM, Joshi SV and Dhar HL. Efficacy of sublingual immunotherapy with multiple allergens in bronchial asthma. Bombay Hospital Journal; 2008; 50, 2:227-231
4. Nuhoglu Y, Ozumut SS, Ozdemir C, Ozdemir M, Nuhoglu C, Erguven M. Sublingual Immunotherapy to House Dust Mite in Pediatric Patients With Allergic Rhinitis and Asthma: A Retrospective Analysis of Clinical Course Over a 3-Year Follow-up Period. J Investig Allergol Clin Immunol; 2006; 17, 6:375-378
5. Bousquet J, Lockey R, Malling HJ. WHO position paper. Allergen immunotherapy: therapeutic vaccines for allergic diseases. Allergy; 1998; 53: 1-42.
6. Passalacqua G, Guerra L, Pasquali M, Lombardi C, Canonica GW. Efficacy and safety of sublingual immunotherapy. Ann Allergy Asthma Immunol; 2004; 93:3-12
7. Bousquet J. Sublingual immunotherapy: validated. Allergy; 2006; 61, 81:5-6
8. Akdis CA, Barlan IB, Bahceciler N, Akdis M. Immunological mechanisms of sublingual immunotherapy. Allergy; 2006; 61,81:11-14
9. Öztürk S, Çalýskaner AZ, Güleç M, Erel F, Kartal Ö, Karaayvaz M, Kutlu A. Effects of allergen specific immunotherapy on the allergens excluded from the treatment. Eur J Gen Med; 2008; 5,4:232-238
10. Geovanni B, Pajno M. Sublingual immuno-therapy, the optimism & the issue. J. Allergy, Clin. Immuno; 2007; Vol. 119, pp.796-801
11. Wikipedia, the free encyclopedia sublingual immunotherapy. [Available at: http:/en / Wikipedia.org/wik/sublingual immunotherapy]

12. Malet A, Valeroa A, Lluch-Péreza M, Pedemonteb C, de la Torrec F. Sublingual immunotherapy with a Dermatophagoides pteronyssinus extract in mass units: assessment of efficacy,safety and degree of compliance. Alergol Inmunol Clin; 2000; 15:145-150

13. Di Rienzo V, Pagani A, Parmiani S, Passalacqua G, Canonica GW. Post-marketing surveillance study on the safety of sublingual immunotherapy in pediatric patients. Allergy; 1999; 54:1110-1113

14. Anthony JF, Helen ES. Sublingual immunotherapy J Allergy Clin Immunology; 2001; 104: 441-444

15. Juniper EF, Guyatt GH, Epstein RS, et al. Evaluation of impairment of health related quality of life in asthma, development of a questionnaire for use in clinical trials. Thorax; 1992; 47: 76-78

16. Sharma S, Kathuria PC, Gupta CK, Nordling K, Ghosh B, Singh AB. Serum immunoglobulin E levels in a case–control study in asthmatic/ allergic patients, their family members, and healthy subjects from India Clinical and Experimental Allergy; 2006; 36:1019–1027

17. Ezeamuzie CI, Ali-Ali SF, Al- Dowaisan A, Khan M, Hijazi Z, Thomson MS. Reference values of total serum IgE and their significance in the diagnosis of allergy among the young adult Kuwaiti population. Clin Exp Allergy; 1999; 29:375–381

18. Guez S, Vatrinet C, Fadel R, Andre C. House dust mite sublingual swallow immunotherapy (SLIT) in perennial rhinitis – a double blind placebo controlled study. Allergy; 2000; 55:369-375

19. Cox L, et al. Allergen immunotherapy: A practice parameter second update. J Allergy Clin Immunol; 2007; 120:S25-85

20. Criticos PS, Norman PS, Feldweg AM. Oral sublingual immunotherapy to allergic rhinitis – a review. J Allergy Clin Immunol; 2010; 148:2126-2145.

21. Bousquet J. Sublingual immunotherapy: from proven prevention to putative rapid relief of allergic symptoms. Allergy; 2005; 60:1-3

22. Stelmach I, Kaczmarek-Woz´niak J, Majak P, Olszowiec-Chlebna M, Jerzynska J. Efficacy and safety of high-doses sublingual immunotherapy in ultra-rush scheme in children allergic to grass pollen. Clin Exp Allergy; 2009; 39:401-408

23. Niu CK, Chen WY, Huang JL, Lue KH, Wang JY. Efficacy of sublingual immunotherapy with high dose mite extracts in asthma: A multicenter double-blind, randomized and placebo controlled study in Taiwan. Respiratory Medicine, Elsevier; 2006;l 100,8: 1374-1383

24. Madonini E, Agostine F, Barra R, Bersa A, Donadio D, et al. Long term & preventive effects of sublingual allergen specific immunotherapy: a retrospective, multicenter study. Int J Immunopath & Pharma; 2003; 16, 1:73-79

25. Bousquet J, Van CP, Khaltaev N. Allergic rhinitis and its impact on asthma. J Allergy Clin Immunol; 2001; 108: S147-334

26. Penagos M, Passalacqua G, Compalati E, Baena-Cagnani CE, Orozco S, et al. Metaanalysis of the efficacy of sublingual immunotherapy in the treatment of allergic asthma in pediatric patients, 3 to 18 years of age. Chest; 2008; 133: 599–609

27. Bahceciler NN, et al. Impact of sublingual immunotherapy on specific antibody levels in asthmatic children allergic to house dust mites. Int Arch Allergy Immunol; 2006; 136: 287-294

28. Wilson DR, Torres L. Durham SR. Sublingual immunotherapy for allergic rhinitis. Allergy; 2005; 60:3-8

29. Wise SK, Woody J, Koepp S, Schloser R. Quality of life outcome with sublingual immunotherapy. Am J Otolaryngology; 2009; 30: 305-311