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ORIGINAL ARTICE

Sublingual versus Subcutaneous Immunotherapy for Egyptian Asthmatic Children: Efficacy, Safety and Cost-Effectiveness Study

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ABSTRACT

Background: In children, indoor allergens play a significant role in the development of asthma. Allergen immunotherapy for the treatment of allergic respiratory diseases has traditionally been administrated by subcutaneous Immunotherapy (SCIT) injections, with certain precautions in administration. Sublingual Immunotherapy (SLIT) could be an alternative to SCIT.

Objectives: To evaluate the efficacy, safety and cost of SLIT versus SCIT among asthmatic children.

Patients and methods: 46 asthmatic children were divided into two groups. Group 1 received SLIT and group 2 received SCIT with close follow up of the patients every 3 months for 9 months regarding the efficacy and safety of allergen immunotherapy using asthma symptoms score, asthma medication scores and quality of life using a validated questionnaire. A cost-effectiveness analysis was done for both routes at the end of the study.

Results: Both routes have nearly equal effects on the course of bronchial asthma. SLIT was the easier route of administration (painless and not needing attendance at the doctor's clinic for each dose). Even though its direct cost was more than SCIT, it eliminates the indirect costs of travel expenses for each dose, stable for a longer time in higher temperatures, with less probability of contamination.

Conclusion: Allergen immunotherapy in addition to controller medicines significantly improves both symptoms and medication scores with minimal side effects in atopic asthmatic children with the advantage of SLIT over SCIT in this age group.

Keywords: bronchial asthma, children, allergen immunotherapy, SCIT, SLIT.

INTRODUCTION

Bronchial asthma is a chronic inflammatory disease affecting the airways and characterized by an exaggerated contractile response of the airways to a variety of stimuli. It can be serious and even life-threatening problem.(1) The burden of asthma is higher than generally recognized, especially in children. It can be distinct in two aspects: first, are the direct costs when patients with asthma utilize the healthcare system using resources which include emergency room visits, visits to outpatient clinics, in addition to the cost of medications.(2) The second aspect is associated with reducing school performance, absence of parents

from the work and transport expenses for receiving health care management; the so-called 'indirect costs'. Patients with moderate allergic disease might not take many sick days per year, but they might still have a suboptimal school performance. Patients in this category cause a large burden because of their high numbers.(3) Studies from developed countries suggest that asthma affects between 11 and 20% of all school age children. The prevalence of asthma among Egyptian children aged 3-15 years was estimated to be 8.2%. Up to one in four children with asthma is unable to attend school regularly because of poor asthma control.(4)

Currently, allergen Immunotherapy (AIT) is the only disease-modifying treatment for allergy since it was introduced by Leonard Noon more than 100 years ago and (5) and it represents a suitable treatment option to modify the progression of airway allergic diseases.(6) Immunotherapy is defined as a prolonged process of gradual repeated administration of extracts of allergen sources to patients with diseases of a known allergic etiology for reducing symptoms by modifying their immunological response so that the affected individuals will react lesser to the involved allergen.(7) Maintenance dose usually achieved after 3 to 6 months. If no improvement is noticed after completing 1 year of adherence to maintenance therapy, reassessment should be done and if the cause of low efficacy cannot be detected, discontinuation is the choice. Duration of maintenance therapy is 3 to 5 years. (8)

The unique aspect of allergen immunotherapy is the ability to induce long term immunological tolerance and hence modifying the disease's natural course.(9) It differs from corticosteroids in their effect on immune system. Corticosteroids are used to modify the cause of the disease through inhibiting pro-inflammatory cytokine secretion by allergen-specific TH2 cells, while AIT switches TH2 allergic IgE mediated response to TH1 IgG mediated anti-inflammatory response.(10) At present, AIT is considered one of the best expressions of personalized medicine in clinical allergy.(11)

There are different routes for immunotherapy administration including classical subcutaneous injection immunotherapy (SCIT) and the later developed sublingual immunotherapy (SLIT) where the allergens are given as drops under the tongue.(12)

In 2009 the World Allergy Organization published the collective evidence showing that Sublingual Immunotherapy (SLIT) could be an alternative to SCIT but this need clinical investigations to characterize optimal techniques.(13) The data and evidence to guide optimum dosing of AIT, optimal allergens mixing options, and the development of quality standardized allergen extracts is still missing. (14)

The aim of this study was to evaluate the efficacy, safety and cost-effectiveness of sublingual immunotherapy versus subcutaneous immunotherapy among Egyptian asthmatic children.

Patients and methods

Study design:

The study was non-randomized controlled trial (Quasi-Experimental study) with 2 groups of allergic asthmatic patients receiving SLIT plus medications or SCIT plus medications. The patients were evaluated in an observation period of 9 months, by assessing the clinical scores and pediatric asthma quality of life questionnaire score at baseline and throughout the study. Skin prick test was done at the beginning of the study. A drop out analysis and cost effectiveness analysis were also carried out. The study design is summarized in figure 1.

Discussing the nature and precautions of each manoeuvre with our patients or their parents was important to confirm that the choice is suitable for their life style and available time and to ensure their adherence to all doses as possible. The study protocol was approved by the Institutional Review Board at the Faculty of Medicine, Zagazig University.

Sample size:

As mean of symptoms score in "sublingual immunotherapy" group (12.1 ± 4) and mean of symptoms score in "Subcutaneous Immunotherapy" group (8.6 ± 3.9) at 80 % power and 95 % Confidence Interval; the estimated sample size will be 46 (23 in each group). (Open EPI)

Patients and diagnosis:

The study was held on at Pulmonology, Allergy and Immunology unit at department of Pediatrics in collaboration with Allergy and Immunology Unit of Medical Microbiology Department at Zagazig University.

Cases of the study were subjected to skin prick test then classified into 2 groups; 23 patients for each. The first group received sublingual allergen immunotherapy (SLIT) and the second received subcutaneous allergen immunotherapy (SCIT).

Inclusion criteria: Children aged from 5 to 12 years with controlled mild to moderate persistent

bronchial asthma diagnosed clinically according to GINA (2022)(15) after proving their allergen sensitivity (with skin prick test) and correlation to clinical history.

Exclusion criteria:

1. Severe uncontrolled asthma .
2. Co-existent autoimmune disease
3. Skin lesions (urticaria or any type of chronic dermatitis).
4. Children previously received allergen immunotherapy.

After their parents' agreement and assignment of informed consent, all patients were subjected to thorough history taking and complete physical examination. The patients were revised for their drug regimen and accurate technique in using their inhalers to make sure of good control of asthma symptoms before the start of the study.

Skin prick test:

Skin prick test was done to provide information about the presence of specific IgE to allergens, applied if there were no contraindications which included inability to discontinue antihistamines, generalized skin disease, adrenergic receptor blocking agent therapy, history of anaphylaxis to previous skin tests or dermographism. Oral steroids - if any- were stopped 48 hours before skin test, and 72 hours if dexamethasone. Local corticosteroids on the arm were stopped for two weeks. Methods and interpretations of the skin prick test were done according to Bernstein et al, 2008. (16)

Allergen extracts used for intradermal skin testing were prepared according to Palmer et al., 1977 (17) from collections of raw material for the following allergens: Multiple molds (Aspergillus Flavus, Aspergillus Nigur, Aspergillus Fumigatus, Candida, Cladosporium), mites (Blomia tropicalis, Dermatophagoides pteronyssinus, Dermatophagoides farina), house dust, hay dust, tobacco, multiple pollens (Phleum pretense “Timothy-grass/Cat tail grass”, ragweed, chenopodium), cat hair, dog hair, horse hair, pigeon and wool. 1g of crude allergenic material was added to 9 ml Coca’s solution to get final antigens prepared in 1/10 Weight/Volume (W/V) dilution; a label of 1:10 weight per volume indicates that 1 g of dry allergen was extracted in 10 mL of buffer.(14)

The mixture was then shaken thoroughly using electric shaker for 2 hours on 2 successive days. Filtration of the mixture in 2 steps; The first was done through Bucher’s funnel using the usual filter paper, and the second filtration was done using Seitz filter. The sterility of the extract was checked by preparation of smears stained with Gram stain and cultivation on nutrient and blood agar to exclude bacterial contamination.(17)

Using these homemade allergen extracts, adopted in the unit are in accordance with ethical standards and have proven efficiently and hadn't caused any adverse influences on human subjects since the unit was officially established in 1989.(18-20)

Positive control was a histamine dihydrochloride solution (10mg/ml). It was used to ensure that the patient was suitable for performing skin prick tests and not taking any medication(s) which may suppress the cutaneous response to the injected allergen extracts.

Negative control was a coca's solution (composed of 20 gm sodium chloride, 16 gm phenol crystals, 11 gm sodium bicarbonate, all dissolved in distilled water to make 4000 ml) to rule out the probability of getting false positive skin response due to dermographism or as a reaction of trauma induced by skin test device.

The histamine positive control result was read at 10-15 minutes after skin prick while the results for allergens at 15-20 minutes.(16) A small itchy lump (wheal) surrounded by a red flare appeared when the patient was allergic.

Allergen immunotherapy:

Allergen immunotherapy was prescribed only for patients with the clinically relevant allergens in both groups and they were offered the two routes of administration with both risks and benefits. Written instructions were given to the patient and/or parents regarding schedule of administration, storage and how to deal with complications.

Active ingredients of AIT were the same allergens constituents used in the skin prick test which were prepared in Allergy and immunology unit and the antigenic extract was standardized as in concentration 1/10 V/W on glycerin - Coca’s solution 5%. One ml contains 50,000 PNU (Protein nitrogen Unit).

Dilutions were prepared under complete aseptic technique under the laminar flow according to the formula [V1 × C1 = V2 × C2] where V1 is the maintenance vial volume, C1 is the maintenance vial concentration, V2 is the stock volume and C2 is the stock concentration. Dilutions for SCIT were prepared using "Coca's solution" in 10 ml vials, while dilutions for SLIT were prepared using

Glycerin 50% from Al-Gomhorria for medical industries company in 20 ml simple bottle with glassy droppers.

We prepared mixes of allergen extracts in the same vial either in the SLIT or SCIT form for those patients how were allergenic for more than one allergen. Only multiple mold immunotherapy was prepared alone without mixing with any other allergen because of its high protease activity which will destruct the other allergens.

The vials contents were labeled and color coded for 3 different dilutions, each was identified according to the updated guide from the American College of Allergy, Asthma and Immunology (ACAAI) and The American Academy of Allergy, Asthma & Immunology (AAAAI) (21) to improve communication between care providers and patients, and to prevent errors in extract administration.

The schedule of treatment doses was not a fixed proposal and was adjusted for each patient by omitting a dose, repeating a previous dose or reducing a dose according to the clinical responses of the patient, the time interval between doses, the presence of a co-seasonal allergen exposure or occurrence of local or systemic reactions following the the preceding dose. For some patients it was accepted not to reach the recommended top maintenance dose, we considered the optimal dose as an individualized dose which resulted in the high clinical efficacy without any major side effects.

I. Sublingual Immunotherapy (SLIT):

❖ **Instruction before administration (given to the patient &/or parents):**

1- Taken daily in the early morning on an empty stomach.
2- Keeping them under the tongue for at least 2 min then swallow and don't eat anything for 15 minutes.
3- Avoiding crunchy cereals as these may cut the tongue and increase the possibility of mouth irritation from the extract.
4- If one morning dose is forgotten, treatment is continued in the next morning at the usual dose.
5- Antihistamines may be used with the dose to decrease local reaction until reaching the maintenance dose.

❖ **Schedule of administration**:

Three months building up/induction doses and maintenance doses to complete total course of 3 years' administration was adopted as the following schedule [Table I-supplementary]:

❖ **If patient missed doses:**

During initiation phase

-If the interruption is <7 days, no modification of the regimen.

-If the interruption is 7-15 days, the dose is reduced by 1 drop for each 5 days of delay.

-If the interruption is >15 days, contact physician for reassessment either to restart from the starting dose or repeat the previous dose.

During maintenance phase

2-4 weeks, reinstituted with half of the dose last given.

4 weeks, contact physician for reassessment either to restart from the starting dose or repeat the skin test.

II. Subcutaneous Immunotherapy (SCIT):

❖ **Instruction before administration (given to the patient &/or parents):**

1- The patient was kept under observation for 20-30 min after injections to observe and record local or general reactions.
2- The extract was injected subcutaneous in outer aspect of the upper arm midway between shoulder and elbow with no massage after injection; we just applied pressure with cotton after injection to prevent leakage.
3- We avoided intradermal or blood vessels injection, and used alternate arm for the series of injects.
4- Before giving each injection we asked about any delayed or immediate reaction following the last dose.

❖ **Schedule of administration:**

Three months building up/induction doses starting with 1:10,000 dilution and biweekly schedule for increasing dose, and monthly increasing concentration. Followed by scheduled maintenance doses (by the highest tolerated concentration in the induction phase 1/100 w/v) to complete total course of 3 years' administration. This was adopted as [Table II-supplementary] schedule.

❖ **If local reaction happened:**

- negative (swelling not redness) < 25 mm, progress according to schedule
- Swelling 26-40 mm, repeat same dose
- Swelling > 40 mm or persist > 24h, return to the last dose which caused no reaction.
- If tolerate the reduced dose, the dose is increased as directed in the building up regimen.

❖ **If patient missed dose (22):**

- In Build-up phase (according to the time interval from last injection): *"Day 0 = time from last injection"*

*0 to 14 days, doses continued as scheduled
*15 to 20 days, dose is reduced by 1 dose
*21 to 28 days, dose is reduced by 2 doses
*29 to 35 days, dose is reduced by 4 doses
*36 days, physician contact for reassessment either to restart from the starting dose or repeat the previous dose.

- Maintenance phase (time interval can be 2, 3 or 4 weeks' interval according to patient schedule)

"Day 0 = time from missed schedule injection (e.g. If shots are every 14 days then day 0 start at day 14 from last injection)"
*0 to 7 days, last dose is repeated
*8 to 15 days, dose is reduced by 2 doses
*16 to 24 days, dose is reduced by 4 doses
*>25 days, physician contact for reassessment either to restart from the starting dose or repeat the skin test.

Clinical Diary card:

We followed up each patient with a diary card on which a symptom score, medication score, and adverse events were recorded. The card items were extracted from. Santanello, et al. (23) Patients were asked for daily record of their symptoms and rescue medication use during the baseline period and for 2 weeks before each visit. Nocturnal and diurnal asthma symptoms were recorded on a four-point scale. These were scored according to Fell's method (24) (25). Patient response to treatment was evaluated before the start of therapy, at 3 months, 6 months and 9 months through recording in the diary card**.**

Pediatric Asthma Quality of life Questionnaire (PAQLQ):

The Arabic version of PAQLQ-A questions was used. They were composed of 23 items comprising 3 dimensions; symptoms, activity limitation & emotional functions.(26) The PAQLQ had a time specification of the previous week; so children were asked to recall their experiences during this period, because this is the maximum length of time over which younger children can remember their experiences with any degree of accuracy(27) and to respond to each question on a 7-point Likert scale.

Calculation of cost-effectiveness

First we calculated the mean total cost per patient for 9 months which was the sum of average costs of allergen extracts, containers, diluents and the printed cards and labels. Cost-effectiveness was calculated by dividing the mean total cost per patient by each of mean asthma symptoms score, mean asthma medication score and mean quality of life questionnaire score. Incremental Cost Effectiveness Ratio (ICER) was also used to calculate the cost of each unit improvement in the studied asthma scores using the equation

Incremental Cost-effectiveness Ratio (ICER) $= \frac{Difference\ in\ cost}{Difference\ in\ effect} = \frac{C1-C2}{E1-E2}$

Statistical analysis

Data were analyzed using Minitab 17.0 statistical software (Minitab Inc., Pennsylvania, USA). Continuous variables were expressed as the mean ± SD & median (range), and the categorical variables were expressed as a number (percentage). Independent sample Student's t-test was used to compare two groups of normally distributed data while Mann Whitney U test was used for non-normally distributed data. Wilcoxon signed ranks test was used to compare two dependent measurements of non-normally distributed data. Friedman test was used to compare more than two groups of non-normally distributed data. Percent of categorical variables were compared using the Chi-square ($\chi 2$) test**.** Cost-effectiveness analysis was done for economic analysis of the allergen immunotherapy utilization. $P < 0.05$ was considered statistically significant.

Results

The two groups were homogenous for demographic characteristics which are are summarized in table 1.

According to the results of skin prick test performed for 80 indicated patients, the allergens which showed high prevalence among the cases were mites by 54.34% of all cases followed by house dust by 52.17% and multiple pollens by 43.47%. [Figure 1].

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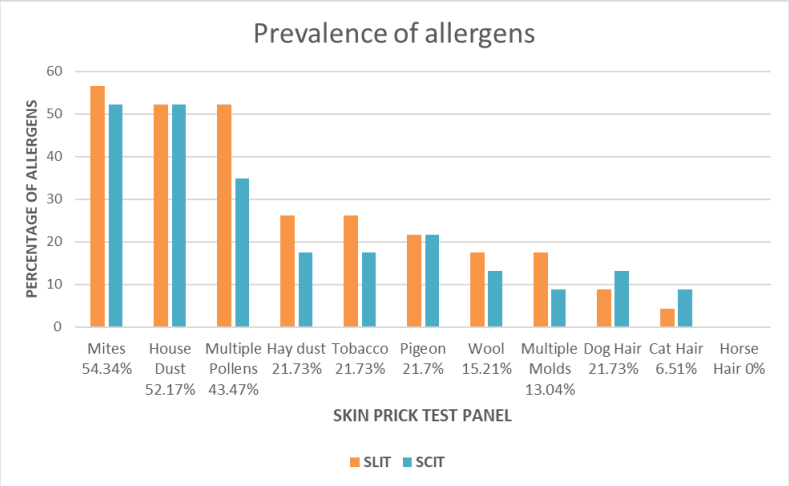

Figure 1: Prevalence of allergens positivity according to skin prick test

Drop-out was not evitable during the study as from the 80 patients included and evaluated through the study about 15 patients were excluded before the start of the treatment because of: negative skin prick test in 13 patients, and sick building syndrome in 2 patients which was confirmed by careful history taking and correlating complete stopping of the symptoms and medications after moving from home. Sick building syndrome generally refers to medical symptoms including increased incidence of asthma attacks with an unclear cause that have a possible relation to the indoor environment according to the definition of the Environmental Protection Agency (EPA).(28) Other drop-out occurred through the 9 months' study at different times; the reasons and timing of drop-out are shown in [Figure I-supplementary].

Forty-six patients completed the 9 months' evaluation for their response to allergen immunotherapy and were non-randomized to receive SLIT (23 patients) or SCIT (23 patients). Planned schedules of SLIT and SCIT were shown in [Tables I and II-supplementary]. The two groups were homogenous for all demographic characteristics which were summarized in [Table 1].

Few side effects were reported during the study, more frequently among SCIT cases (13.04%) in the form of local inflammation at the site of injection, while in SLIT group only one patient experienced mild vomiting

Table 1: Comparison between the studied groups as regard demographic data

Demographic data	**SLIT** (N=23) Mean ± SD		**SCIT** (N=23) Mean ± SD		**Test**	**P-value (Sig.)**
Weight (kg)	21.69 ± 4.723		21.47 ± 4.315		0.163*	0.871 (NS)
Age (Y)	6.69 ± 1.987		6.52 ± 1.533		0.332*	0.741 (NS)
Sex	No.	%	No.	%		
Male	15	65.21	14	60.86	0.093§	0.760 (NS)
Female	8	34.78	9	39.13		

*Independent Student's t-test. § Chi-square test.

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Symptoms, medications and quality of life scores of the two groups were assessed initially and throughout the period of the study. The response to allergen immunotherapy in both groups showed variable improvement after 3, 6 and 9 months [Figure 2] and [Tables 2,3,4]

Cost effectiveness analysis for nine months of allergen immunotherapy administration was in favor of SCIT regarding direct cost of the vaccine [Table 5].

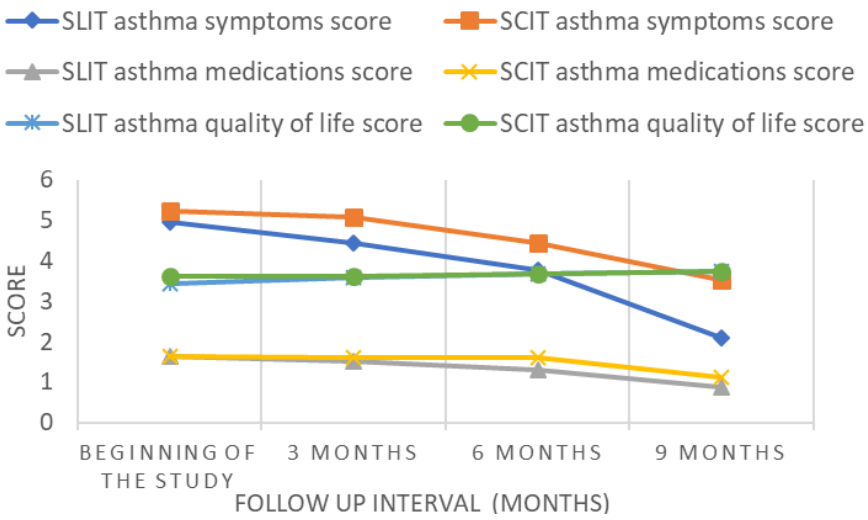

Figure 2: Symptoms, medications and quality of life scores of the two groups in response to AIT through nine months' study.

Table 2: Asthma symptoms scores of the two groups during the nine months follow up period

Asthma symptoms score	**SLIT (N=23)**	**SCIT (N=23)**	**Test**	**P-value (Sig.)**
At the beginning (Before Immunotherapy administration)				
Mean ± SD	4.96 ± 1.94	5.22 ± 2.17	523.5*	0.717 (NS)
Median	6	6		
3 months				
Mean ± SD	4.43 ± 1.78	5.09 ± 2.11	497.5*	0.3505 (NS)
Median	3	6		
Test (vs the beginning)	17.5§	1§		
P-value (Sig.)	0.173 (NS)	1 (NS)		
6 months				
Mean ± SD	3.78 ± 1.35	4.43 ± 2.37	494.0*	0.3122 (NS)
Median	3	3		
Test (vs the beginning)	45.0§	44.0§		
P-value (Sig.)	0.009 (HS)	0.103 (NS)		
9 months				
Mean ± SD	2.09 ± 1.68	3.52 ± 2.15	447.5*	0.0421 (Sig.)
Median	3	3		
Test	26.62 ¦	11.06 ¦		
P-value (Sig.)	<0.0001(HS)	0.0114 (Sig)		

*Mann-Whitney Test, § Wilcoxon signed-rank test, ¦ Friedman test

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Table 3: Asthma medication scores of the two groups during the nine months follow up period

Asthma Medications score	SLIT (N=23)	SCIT (N=23)	Test	P-value (Sig.)
At the beginning (Before Immunotherapy administration)				
Mean ± SD	1.652 ± 0.714	1.652 ± 0.775	544.5*	0.9387 (NS)
Median	2	1		
3 months				
Mean ± SD	1.522 ± 0.730	1.609 ± 0.783	526.0*	0.7584 (NS)
Median	1	1		
Test (vs the beginning)	6§	6§		
p-value (Sig.)	0.181(NS)	1 (NS)		
6 months				
Mean ± SD	1.304 ± 0.470	1.609 ± 0.783	480.5*	0.1912 (NS)
Median	1	2		
Test (vs the beginning)	36§	16§		
p-value (Sig.)	0.014 (Sig)	0.8 (NS)		
9 months				
Mean ± SD	0.870 ± 0.548	1.130 ± 0.694	491.5*	0.2866 (NS)
Median	1	1		
Test	17.8¦	10.12¦		
P-value (Sig.)	0.0005 (HS)	0.0176 (Sig)		

*Mann-Whitney Test, § Wilcoxon signed-rank test, ¦ Friedman test

Table 4: Pediatric asthma quality of life questionnaire scores of the two groups during the nine months follow up period

Quality of life questionnaire score	SLIT (N=23)	SCIT (N=23)	Test	p-value (Sig.)
At the beginning (Before Immunotherapy administration)				
Mean ± SD	3.448 ± 0.637	3.622 ± 0.649	502.5*	0.41 (NS)
Median	3.4	3.6		
3 months				
Mean ± SD	3.583 ± 0.584	3.626 ± 0.661	531.0*	0.8433 (NS)
Median	3.6	3.5		
Test (vs the beginning)	0§	12.5§		
p-value (Sig.)	0.001 (sig.)	0.866 (NS)		
6 months				
Mean ± SD	3.678 ± 0.575	3.678 ± 0.672	538.0*	0.9650 (NS)
Median	3.7	3.5		
Test (vs the beginning)	10.5§	15.5§		
p-value (Sig.)	< 0.0001 (HS)	0.039 (Sig)		
9 months				
Mean ± SD	3.730 ± 0.576	3.730 ± 0.677	539.0*	0.9825 (NS)
Median	3.7	3.6		
Test	40.66¦	21.87¦		
p-value (Sig.)	< 0.0001 (HS)	<0.0001 (HS)		

* Mann-Whitney Test, § Wilcoxon signed-rank test, ¦ Friedman test

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Table 5: Direct cost effectiveness analysis for nine months of allergen immunotherapy administration

Cost Effectiveness analysis	SLIT (N=23)	SCIT (N=23)
Mean cost for 9 months treatment		
Average cost of Allergen extract	115 L.E.	27.07 L.E.
Average cost of containers	2.26 L.E.	2.17 L.E.
Average cost of Instruction cards & Labels	4.89 L.E.	5.22 L.E.
Average cost of Diluent	11.85 L.E.	36.39 L.E.
Mean total Cost per patient (Average)	134 L.E.	70.85 L.E.
Effectiveness After 9 months treatment		
Mean asthma symptoms Score	2.09	3.52
Mean asthma medication score	0.87	1.13
Mean quality of life questionnaire score	3.73	3.73
Cost/Effectiveness C/E		
Asthma symptoms Score	64.11	20.12
Asthma medication score	154.02	62.69
Quality of life questionnaire score	35.92	18.99
Incremental Cost Effectiveness Ratio (ICER)*		
Asthma symptoms Score	44.16	
Asthma medication score	2.4	

Discussion

Allergic diseases are increasingly prevalent problems affecting up to one-third of the general population in industrialized countries**.**(25) Asthma is considered as the most common chronic diseases of childhood. Many patients with asthma receive treatment with pharmacotherapy such as bronchodilators and inhaled corticosteroids. Such medications are effective in reducing symptoms and controlling the disease, but do not address the underlying allergy. The unique aspect of allergen immunotherapy is the ability to modify the natural course of disease by inducing long term immunological tolerance.(9)

As regard the relative clinical efficacy of SCIT and SLIT, when each was compared with placebo separately, results of meta-analyses suggested great efficacy of both routes of administration (29). Studies on pediatric patients indicates that both SCIT and SLIT improve asthma symptoms and reduce drug requirements (30). However, head-to-head studies with well-defined effective doses by the 2 routes were still needed.

From that point of view, this study was held to evaluate and to compare the efficacy and safety of SCIT versus SLIT on allergic asthmatic children. The evidence for the efficacy of AIT for AR is limited in children younger than 5 years of age, also there is evidence of risk with uncontrolled asthma (31). So, in our study we included children aged from 5 to 12 years with controlled mild to moderate persistent bronchial asthma; they were 23 patients with mean age 6.69 ± 1.98 years who received SLIT and 23 matched patients with mean age 6.52 ± 1.53 years who received SCIT. The patients included in each group were chosen non-randomly because of the non-feasibility to use randomized sampling. SCIT needed to be given at clinic twice weekly for probability of side effects. So, home address in relation to our hospital, parents' and/or patients' preference, cooperation and educational status were considered in choosing the route of administration of allergen immunotherapy.

All allergen products in the market are manufactured by aqueous extraction of allergenic source materials obtained from natural raw materials, such as pollens, house dust mite cultures, insect venoms or animal hair and/or dander. Those raw materials are varying in composition and, therefore, it is better to standardize the materials and methods for determining the major allergen content of different AIT products (32). The standardization includes all

aspects of the manufacturing process, from selection and collection of raw materials, ensuring qualifications of collectors, preparation and storage of extract, to the validation of assays and reagents.(33)

References and control extracts are used to control of the variation in the natural source of the handled material. In Europe, each manufacturer forms this/her own in-house reference preparation, which must be matched. Different manufacturers use different raw materials, production processes, and standardization procedures, so, allergen products are not generic, they differ in their composition, ability of IgE-binding, and level of quality control. No international standards are available. This means that products from different manufacturers can perform differently in patients and, consequently, clinical results cannot be concluded directly from one allergen product to another. However, in the USA, the US Food and Drug Administration (FDA) releases standards and assays to be followed by all manufacturers.(34)

Quality of an allergen extract depends on many criteria including purity, potency, stability, sterility and safety. As regard potency in allergen immunotherapy extract preparation, it can be expressed by two formulae; the first one is weight/volume W/V formula which is used without detection of the protein concentration inside the antigenic materials. At this point it is a non-standardized extract. The second formula is protein nitrogen unit (PNU) formula which detects protein concentration inside the antigenic materials, hence it is called standardized extract.(14) Most of the commercial formula are non-standardized and expressed as W/V.(34)

From all the above, taking in our consideration the possibility of different antigenic properties in the different allergens due to different environments, we choose to measure the efficacy and safety of our own home-made allergen immunotherapy which has been prepared using weight/volume W/V formula in the Allergy Unit of Medical Microbiology and Immunology Department used for allergic asthmatic children managed at Pediatric Pulmonology, Allergy and Immunology Unit, Department of Pediatrics at Zagazig University. The antigenic extract was standardized as in concentration 1/10 V/W. One ml contains 50,000 PNU (Protein nitrogen Unit).

As the common starting SCIT dilutions for the building-up concentrate are 1:10,000 (vol/vol) or 1:1,000 (vol/vol) and the most commonly used schedule is for increasing doses of allergen immunotherapy extract to be administered 1 to 3 times per week.(Recommendation statements 47 and 48 with strength of recommendation D)(7) We practiced three months building up/induction doses starting with 1:10,000 dilution with bi-weekly schedule for increasing dose and monthly increasing concentration. Followed by scheduled maintenance doses to complete total course of 3 years [table II-supplementary]. On the other hand, more gradual schedule for increasing allergen extract concentrations was used in other study in Atta et al. study. (19)

Allergen immunotherapy extracts used for the induction phase usually consist of three or four 10-fold dilutions of the maintenance concentrate and rate of increasing the volume depends on the patient's response and sensitivity to the extract and history of previous adverse reactions (7).

Standard practice of AIT in the United States allows using mixes of allergen extracts to treat multiple allergen sensitizations. A 2019 survey in the United States found that 63% of AIT providers used 6 or more allergens in their prepared SCIT vials (14), in addition that FDA permitted limited quantities to be made by the allergists and other physicians who mixed drug and/or biologics in their offices for selected individual patient in agreement with the US pharmacopeia chapters that are appropriate to pharmaceutical compounding (35). hence we prepared mixes of allergen extracts in the same vial either in the SLIT or SCIT form for those patients how were allergenic for more than one allergen.

Despite a lack of FDA-approved aqueous SLIT preparations in the United States, the American Academy of Allergy, Asthma, and Immunology survey reported that US aqueous SLIT prescriptions among respondents increased from 5.9% to 11.4% between 2007 and 2011, and 86%

of respondents reported prescribing commercially available SCIT extracts for off-label use as SLIT(36-38). In our practice, the active ingredients of AIT were the same allergens constituents used in the skin prick test. Dilutions for SCIT were prepared using "Coca's solution"5% in 10 ml vials, while dilutions for SLIT were prepared using Glycerin 50% in 20 ml simple bottle with glassy droppers.

Adverse reactions to AIT can be divided into local (limited to the site of administration)(39) and systemic (wheezing, urticaria, anaphylaxis, fatal reactions).(6)

Regarding the safety of allergen immunotherapy, in the present study, we didn't report serious systemic adverse events in patients receiving immunotherapy in both groups. In a recent prospective European survey involving 762 children and 801 adolescents receiving AIT, a total of 29 reactions have been reported, of which 23 with SCIT and 6 with SLIT, involving 3 cases of anaphylaxis, all related to SCIT. This highlights the importance of patient observation after AIT administration,(40) so, we observed our patients for at least 30 minutes according to current recommendations.

One of our patients (represents 4.34% of cases) in SLIT group complained of local reaction in the form of mild vomiting occurred once or twice within six hours after receiving the dose only during the first month of induction phase and didn't recur later. Three patients (13.04% of cases) in SCIT group complained of local inflammation at the site of injection in the form of intolerable swelling and erythema which was related to the first few injections of the 1 ml dose of 1/100 dilution injections and became tolerated afterwards, while there was no significant difference between both groups as regard occurrence of side effects. This was in agreement with other studies discussing the local reactions of allergen immunotherapy(41) and the relation of mode of action with their safety profile (42). Local reactions were very common but it was not a common reason for discontinuation.(7) AIT was well tolerated by children/adolescents and regarded as very good or good by 93% of the young population with allergic asthma. (6)

As regard the efficacy of the allergen immunotherapy, the study focused on three aspects; asthma symptoms score, asthma medications score and quality of life. Each of those parameters was assessed at the beginning and every three months during the study.

Regarding asthma symptoms score in our study [Table 2], it started to show significant improvement after six months of administration of SLIT. After nine months there was a significant improvement in symptoms score in both groups with significant difference between them in favor to SLIT. On the other hand, Saporta 2012 and Deb et al.2012 revealed approximate improvement of asthma symptoms score in both methods of AIT.(25, 43)

In concordance with our results, significant improvement in asthma symptoms score after nine months of administration of sublingual immunotherapy (9) and subcutaneous allergen immunotherapy (44) was reported, and even earlier significant improvement in the daily symptom scores after only 16 weeks of administration of SLIT and SCIT respectively was observed. (45, 46)

Regarding asthma medications score, [Table 3] this study showed that asthma medications score started to show significant improvement after six months in SLIT group with no significant difference between the two routes and this improvement continued significantly at the nine months' evaluation, while the improvement occurred after nine months in SCIT group without significant difference between both groups. However, the improvement in medication score in the early months of immunotherapy couldn't be considered as insignificant in more than a study (25, 43, 45, 46). Our results were supported with other study which stated significant improvement in the medication score in each method of AIT (47). Nevertheless, other studies could not find significant reduction in asthma medication score after nine months' administration of sublingual immunotherapy.(48, 49)

In the contrary to our results of earlier improvement in the symptoms and medication

scores among the SLIT asthmatic group, a recent prospective study documented earlier therapeutic effect of SCIT than SLIT in pediatric patients treated by standardized house dust mite extract for allergic rhinitis detected by specific symptoms and medication scores. (50)

In the present study, Pediatric Asthma Quality of Life Questionnaire (PAQLQ) score has been assessed [Table 4]. We reported significant individual improvement in each group from the baseline scores until the nine months' re-evaluation. The patients in group 1 (SLIT) showed earlier improvement in total score after 3 months of administration while the patients in group 2 (SCIT) started to show significant improvement in the total score after six months. These results agreed with Olivier et al., 2013 and Uriarte, 2014 who observed significant improvement in total quality of life questionnaire score after six months of SLIT and SCIT administration respectively.(51, 52) From other point of view, a systematic review and meta-analysis studying allergen immunotherapy for allergic asthma concluded that subcutaneous immunotherapy (SCIT) improved quality of life and decreased allergen-specific airway hyper-reactivity, but this was not the case for sublingual immunotherapy (SLIT). (53)

Our findings suggested that both the SLIT and SCIT are equally effective in improving the quality of life in patients with allergic asthma with no significant difference in PAQLQ scores between the two groups at any time of evaluation, and with nearly equal scores for SLIT and SCIT groups at the nine months' re-evaluation (3.730 ± 0.576), taking in consideration that response to PAQLQ is subjective and somewhat difficult for younger children. Parents helped their young children in scoring their symptoms and use of medication. Higher values of quality of life scores were recorded in previous study using the same questionnaire for specific immunotherapy asthmatic children with older age (7-18 years); their score ranged from (2.6-6.9) with 5.0 ±l.l mean ±SD.(54)

Treatment by allergen immunotherapy needs at least a three years' period, but as the objective of the treatment is induction of immunological tolerance, the effect of therapy might persist several years afterward. So, the total healthcare cost of the treatment could be regarded as an investment, taking in consideration the cost savings over the following years because of disease modification.(55) The societal benefit of AIT is related to cost savings caused by decreased medications consumption, fewer visits to general practitioners and specialists, and improved productivity gains. In addition, disease modification can lead to a reduced risk of developing more severe asthma, which is of societal benefit because of the high costs of management and related lost school days and work-days' absence for the care-givers.(56)

Despite the use of widely varying study designs, patient samples and methodologies, the economic analyses of immunotherapy conducted before have consistently shown that immunotherapy reduces direct and indirect costs.(3) A German randomize control trial (RCT) compared SCIT with standard care for 65 patients with three years of follow-up found that SCIT was more expensive but performed better than standard care alone on the disease-specific outcome measure.(57) Another Italian RCT -with five years of follow-up for 70 patients-compared SLIT with standard care in asthma and rhinitis patients and reported that patients on SLIT cost less and experienced less symptoms than those on standard care.(58) The updated guideline of Korean Academy of Asthma Allergy and Clinical Immunology (KAAACI) stated with high evidence that both SCIT and SLIT are equally effective in children, and the choice between them depends on the preference, cost, and compliance of the patient or caregiver(30).

So, it was important to conduct an analysis to indicate which intervention provides higher value, where its health benefits justify its costs. The methodology utilized here was the cost-effectiveness analysis, which compares the health benefits and the direct costs of the sublingual allergen immunotherapy and the subcutaneous allergen immunotherapy administration for 9 months' duration. Incremental Cost Effectiveness Ratio (ICER) was also used to calculate the cost of each unit improvement of the studied asthma scores. To our knowledge this was the first

Egyptian study discussing the cost-effectiveness of AIT for asthmatic children calculated by Egyptian Pound (LE).

Our data showed that SCIT was more cost-effective compared to SLIT at the level of asthma symptoms, medications and quality of life scores. The ICER revealed that the cost was 44.16 L.E. for every unit improvement in the symptoms score, 2.4 L.E. for every unit improvement in the medication score, knowing that this was the net non-profit cost for 9 months. It was unfeasible to calculate the ICER for the quality of life score as both SLIT and SCIT groups reached nearly the same mean value. The analysis depended on the direct cost of the immunotherapy [Table 5]. From other point of view, Pokladnikova et al stated that SLIT represents a less expensive alternative relative to subcutaneous administration from all perspectives when consider the indirect costs.(59)

However, from a patient's point of view, SCIT offers a less expensive alternative for patients who do not experience indirect costs in the form of doctor visiting for each dose, loss of income and transport costs associated with treatment, the more liability of contamination and impurity, the more liability to lose potency over time which is influenced by many factors such as storage temperature, presence of stabilizers and bactericidal agents, presence and concentration of proteolytic enzymes.

Glycerin 50% is a stabilizer used in diluting SLIT not in SCIT and this offers more stability for the antigens even in higher temperatures. Aqueous extracts and diluted extracts in normal saline are stable at room temp for a few days while glycerinated extracts are very stable up to about 40 °C.(21) Change in temperature due to different causes e.g. repeated or prolonged cutting the electric current make it more possible to affect the stability, clarity and potency of SCIT than SLIT especially in the diluted doses. This put more cost to change the vial if had to be discarded for any cause.

Putting in mind all these considerations when we add the indirect costs to our evaluation, SLIT could be more cost effective alternative than SCIT.

The relative small sample size, and the limited 9 months' period of follow up are considered limitations of this study.

Conclusion

Allergen immunotherapy in addition to controller medicines significantly improves both symptoms and medications and quality of life scores with minimal side effects in atopic asthmatic children.

SLIT has many advantages over SCIT which include: early effect in the course of the disease, more tolerability, easier route of administration (painless and doesn't need attendance to doctor's clinic for each dose), eliminate cost of transport for each dose, more stability and resistance for longer time in higher temperatures, and lesser probability of contamination.
Sublingual immunotherapy has a higher calculated direct cost however the study didn't include the accurate indirect cost which was important to be considered even if it was not precisely calculated.

Recommendation

In spite of nearly similar efficacy of SCIT and SLIT, allergen immunotherapy is preferred to be used by the sublingual route when indicated for allergic asthmatic children because of its advantages of earlier effect in the course of the disease, more tolerability and relative total cost-effectiveness. More studies are needed to compare the efficacy, safety and cost of allergen immunotherapy by different routes of administration for longer durations and long-term efficacy after stopping AIT, more studies of the overlap between different asthma controller medications and AIT. Also we need more economic studies to evaluate the actual indirect costs of AIT in different sittings.

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Supplementary material

Table I: Schedule of SLIT:

Vial	Conc.	Dose	Frequency	Duration	Time
RED [Starting dose]	1/250 W/V	3 drops	Once daily	For a week	One month
		5 drops		For a week	
		7 drops		Till the end of the 1st bottle	
YELLOW	1/125 W/V	3 drops		For a week	One month
		5 drops		For a week	
		7 drops		Till the end of the 2nd bottle (15 ml)	
GREEN	1/50 W/V	3 drops		For a week	One month
		5 drops		For a week	
		7 drops		Till the end of the 3rd bottle (15 ml)	
GREEN [Maintenance concentrate]	1/50 W/V	7 drops	Daily	Till the end of the 4th bottle (15 ml)	One month
		7 drops	3 times weekly	Till the end of the 5th bottle (15 ml)	2 months
		7 drops	Twice weekly	Till the end of the 6th bottle (15 ml)	3 months
		7 drops	Once weekly	Till the end of the 7th bottle (15 ml)	4 months
		7 drops	Once every 2 weeks	Till the end of the 8th bottle (15 ml)	8 months
		10 drops	Once monthly	Till the end of the 9th & 10th bottles (10 ml for each) to ensure allergen stability	15 months

W/V: Weight/Volume

Table II: Schedule for SCIT:

Dose / Vial	1st dose	2nd dose	3rd dose	4th dose	5th dose	6th dose	7th dose	8th dose	Frequency	Duration
RED [Starting dose] (1/10.000 w/v)	0.20 ml	0.40 ml	0.60 ml	0.80 ml	1 ml	1 ml	1 ml	1 ml	twice weekly (doses are not repeated)	1 month
YELLOW (1/1000 w/v)	0.20 ml	0.40 ml	0.60 ml	0.80 ml	1 ml	1 ml	1 ml	1 ml		1 month
GREEN (1/100 w/v)	0.20 ml	0.40 ml	0.60 ml	0.80 ml	1 ml	1 ml	1 ml	1 ml		1 month
GREEN (1/100 w/v) **[Maintenance concentrate]**	1 ml for 6 doses								weekly	1.5 months
	1 ml for 6 doses								every 2 weeks	3 months
	1 ml for 6 doses								every 3 weeks	4.5 months
	1 ml monthly and stay at this interval								monthly	2 years

W/V: Weight/Volume

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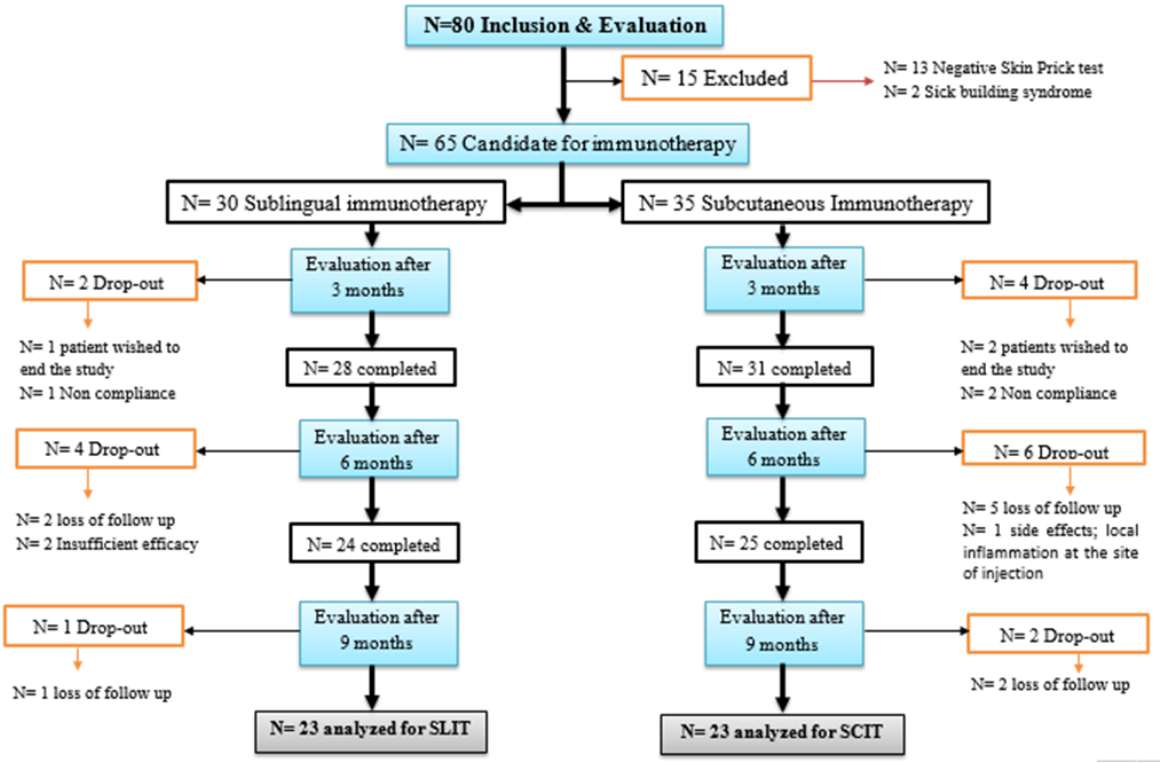

Figure I: Study design and drop-out

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