*Original article*

Paediatrics Today 2012;8(1):47-57
DOI 10.5457/p2005-114.37

# COMPARISON OF CLINICAL EFFICACY AND SAFETY SUBCUTANEOUS AND SUBLINGUAL IMMUNOTHERAPY IN KUWAITI SCHOOLCHILDREN WITH SEASONAL ALLERGIC RHINITIS

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**Received:** July 14, 2011
**Accepted:** November 29, 2011



**Objective -** To compare the clinical efficacy and safety of sublingual immunotherapy (SLIT) vs. subcutaneous immunotherapy (SCIT) in Kuwaiti schoolchildren with seasonal allergic rhinitis (SAR), sensitive to pollens of Salsola kali and Bermuda grass.

**Patients and methods -** The study was single blinded. Patients and Methods: Eight-two schoolchildren, 9-14 years old, diagnosed with SAR due to sensitization to local pollen allergens (Salsola kali, Bermuda grass or both), who fulfilled the inclusion criteria, were randomly selected (1:1) to receive either SLIT (n=38), Staloral; Stallergenes SA, Antony France, or SCIT (n= 44), Alustal, from the same manufacturer, as a 3 year treatment course. Twenty-five patients from the SLIT and 34 from the SCIT group completed the treatment. Clinical efficacy was evaluated on a yearly basis, during the pollination period, by total clinical symptom scores (TCSS) and reduction in medication consumption. Adherence to the treatment, as well as safety profile of both modes of immunotherapy was compared.

**Results -** There was no difference in adherence to the treatment between the 2 groups. Our study demonstrated that SCIT had a tendency for faster clinical improvement than SLIT, but at the end both were equally effective. Significant reduction in drug use (>50%) in the 1st treatment year was seen only in the SCIT group ($p < 0.02$). In the end, there was no significant difference between the two groups ($p < 0.4$). A mild systemic reaction (grade 2) was seen in 1 patient in the SCIT group, while local reactions were seen in both groups.

**Conclusion -** Our study demonstrates that SLIT is a valid alternative to SCIT in terms of clinical efficacy and safety, and can be safely used in schoolchildren sensitive to pollen allergens.

**Key words:** AIT=Allergen immunotherapy, SLIT= Sublingual immunotherapy, SCIT= Subcutaneous immunotherapy, SAR= Seasonal allergic rhinitis.

## Introduction

Allergen immunotherapy (AIT) has been widely used with proven clinical efficacy to treat patients with allergic rhinitis, and mild to moderate asthma (1-6). AIT is considered as the only specific treatment of allergy, with a capacity to decrease allergic inflammation, reduce clinical symptoms, and modify the natural course of the disease (7-10). AIT is the practice of administering increasing doses and concentrations of allergen vaccine in patients to achieve a state of hypo-sensitization, to develop tolerance and thereby to reduce clinical symptoms, which occur during the natural exposure to the offending allergen(s). At present it is considered that AIT with a well-standardized allergen vaccine in optimal doses, over a long enough period of time, should result in a good clinical outcome.

Administration of the allergen by repeated subcutaneous injections (SCIT) is the old, well established and classical form of AIT. Although highly effective, disadvantages such as frequent clinic visits, poor compliance, discomfort from repeated injections, and above all, the possibility of severe systemic adverse reactions such as anaphylaxis (10) have prompted the search for an alternative method of administration. At present, there is consensus that SLIT is the only valid alternative to SCIT (11). During the last 20 years, SLIT generated a great deal of interest, especially in the pediatric population, and currently appears as a useful and attractive treatment modality in terms of both clinical efficacy (12-16) and safety (17-22). Systemic review and meta-analysis support the efficacy of SLIT in allergic rhinitis patients, both in adults and children (23). Passalacqua et al. (24) and others (9, 25) suggest that immune-modulatory response in SLIT is similar to that seen in the subcutaneous route. However, well designed controlled studies, which directly compare SLIT to SCIT (12, 16, 25-27) are still lacking. Due to conflicting results with SLIT shown in some studies (20), more thorough and advanced assessment is required.

In this study we compared the clinical efficacy and safety aspects of SLIT vs. SCIT, in Kuwaiti schoolchildren with allergic rhinitis.

## Patients and methods

A parallel, randomized, single - blinded, study was undertaken in a group of 82 schoolchildren, 29 boys and 53 girls, aged 9-14 years, with physician diagnosis of SAR. Patients were recruited at the Allergy Department, Al-Rashed Allergy Centre, from September 2003 to October 2004. After baseline evaluation, subjects who fulfilled the inclusion criteria were randomly allocated (1:1) to receive, either SCIT (n=44) or SLIT (n=38). In the SCIT group the active product used was standardized Salsola kali and Bermuda grass allergen extract adsorbed on aluminum hydroxide (Alustal) from Stallergenes SA, Antony, France, while in a SLIT, a protocol of drops of the same standardized allergen extract (Staloral), from the same manufacturer, was used.

In order to avoid bias, the selected patients were not informed exactly about the nature of ingredients and their effects, either in the SLIT or the SCIT group. They were assigned 3 years of treatment with immunotherapy, starting 4 months before the commencement of the second next pollen season (September-October, 2005). Prior to enrolment to the study informed consent was obtained from each patient, in both the SCIT and SLIT groups.

The inclusion criteria were: clinical history of severe seasonal rhinitis and/or conjunctivitis during at least two previous pollen seasons, with poor response to drug treatment, and positive skin prick test (SPT) to maximum 2 local pollen allergens (Salsola kali and /or Bermuda grass). SPT was per-

formed with a battery of inhalant allergens provided by Stallergenes. The result of SPT was considered to be positive if the wheal diameter is 3 mm or more than the negative control, 15 minutes after testing.

All patients were on the same drug treatment: Fluticasone nasal spray 50 mcg/puff: 2puffs/twice daily, Desloratadine 5 mg / once daily and /or Chromoglycate eye drops: 20mg/ml / 2-3 drops three to four times daily. The use of bronchodilators was also allowed in the case of asthma symptoms. At baseline, pollen related asthma was ruled out by the absence of a significant cough, shortness of breath, and a normal FEV1 (>80%) in the peak of the pollen season. During the peak of pollination, patients self-recorded daily symptoms and medication consumption in a diary card, at baseline and during the 3 treatment years. Adverse reactions, if any, were also recorded.

Total clinical symptom score (TCSS) was calculated as the sum of individual scores: sneezing, itching, runny and blocked nose, and/or watery and itchy eyes, cough and wheezing. Each particular symptom ranged from 0-3: 0= no symptoms, 1= mild, 2= moderate and 3 = severe symptoms. At baseline TCSS should be ≥ 10. TCSS was calculated each year at the peak of pollination and compared with the baseline. Reduction in drug consumption was assessed as a percentage of reduction, in comparison with the treatment before AIT: no reduction, reduction <50% = if the patient reduced either antihistamines or INS, and reduction >50% = reduction of both drugs. The overall personal patient's perception of AIT efficacy at the end point was expressed as: poor or mild, good or very good response. Exclusion criteria were: polysensitization previous treatment with AIT, persistent asthma and presence of other chronic diseases.

In both SCIT and SLIT we used Bermuda grass, Salsola kali or a mixture of both. Throughout the study, the allergen vaccine was provided by the same manufacturer. In the SCIT group allergen injections were given twice weekly during the build-up phase. When the maximal dose of maximal concentration (0.8 ml/300 IR) was reached, the same dose was given as a once monthly injection for 3 consecutive years. At the peak of pollination, the maintenance dose was reduced by 25%. The peak pollen season was assessed in the aerobiology laboratory on the basis of the pollen count from pollen traps placed at several locations in Kuwait. While replacing the new vial, the dose was reduced by 50%, and then gradually increased until the full maintenance dose was reached. All the patients were observed 20 minutes after each injection due to possible systemic reactions. The reaction was graded according to the WHO position paper from grade 1 to 4 (10).

SLIT is a glycerinated solution prepared to be administered under the tongue. Patients were allowed to take the vaccine home and advised to use it before breakfast. They were asked to place the drops under the tongue for two minutes and then swallow. During the short time of the build–up phase (11 days) the dose and concentration (IR/100, followed by IR/300) was increased gradually until the maximal dose of maximal concentration (8 drops/IR/300) was reached. The maintenance dose (4 drops IR/300) was taken daily for the next 3 years. Systemic and local adverse reactions were also analyzed.

**Statistical analysis**

The statistical package SPSS 17, for Windows (Chicago, IL, USA) was used for analysis. The Chi-square test was used to test the differences between the 2 groups. Paired sample t-test was used to compare two dependent samples within the group. A value of $p < 0.05$ was considered statistically significant.

## Results

Fifty-nine patients, 25/38 (65.7%) from the SLIT and 34/44 (77.2%) from the SCIT group completed the 3 years course of treatment. There was no significant difference between the groups in respect to age (13.6 ± 0.4 in SLIT and 12.5±0.5 years old), gender, duration of disease, and incidence of sensitization to Salsola kali, Bermuda grass or both. Drop out from treatment was higher in the SLIT (34.3%) than in the SCIT group (22.8%) (Table 1).

The clinical symptom score taken in the 1st pollen season on immunotherapy showed slightly better results in the SCIT group (11.8 ± 0.2 to 7.3 ± 0.2 vs. 11.5 ± 0.2 to 10.2 ± 0.1 in SLIT group; p=0.05), but equal efficacy in both groups was seen at the end point (6.8 ± 0.3 in SLIT and 6.0 ± 0.2 in SCIT group: p <0.001) (Table 2).

A significant reduction in drug consumption (>50%) in the 1st treatment year was seen only in the SCIT group (58% in SCIT vs. 24% in SLIT; p <0.02), while in the 2nd and 3rd treatment years, there was no significant difference (p=0.62 and p=0.46 respectively). Only a small number of patients (8% in SLIT and 2.9% in the SCIT group) could not reduce either INS or antihistamines (Table 3).

The overall clinical benefit of immunotherapy at the end point, as assessed by the patient's personal satisfaction, was similar in both groups. Good/very good response was found in 72.0% in SLIT and 70.6% in SCIT; p=0.90) (Table 4).

**Table 1** Patient characteristics

| Patients | Treatment groups | | | |
|---|---|---|---|---|
| | SLIT | SCIT | Total | p value |
| Patients at baseline (n) | 38 | 44 | 82 | - |
| Patients at endpoint (n; %) | 25/38 (65.7) | 34/44 (77.2) | 59 | 0.20 |
| Boys | 14 (56.0) | 15 (44.0) | 29 | 0.20 |
| Girls | 11 (44.1) | 19 (55.9) | 30 | 0.20 |
| Age (mean ± SE) | 13.6 ± 0.4 | 12.5 ± 0.5 | - | 0.60 |
| Disease duration (n; %) | | | | |
| > 2 y | 11 (44.0) | 9 (26.5) | 20 | - |
| > 5 y | 14 (56.0) | 25 (73.5) | 39 | - |
| Seasonal symptoms (n; %) | | | | |
| March-May | 0 (0.0) | 1 (3.0) | - | - |
| September – October | 8 (32.0) | 11 (32.4) | - | - |
| Both | 17 (68.0) | 22 (64.6) | - | 0.20 |
| Allergen vaccine (n; %) | | | | |
| Bermuda grass | 3 (12.0) | 7 (20.6) | - | - |
| Salsola Kali | 9 (36.0) | 14 (41.2) | - | - |
| Mix of both | 13 (52.0) | 13 (38.2) | - | 0.20 |
| Adverse reaction | | | | |
| Local | 5 (20.0) | 5 (14.7) | - | - |
| Systemic | 0 (0.0) | 1 (2.90) | - | - |

SLIT= Sublingual immunotherapy; SCIT=subcutaneous immunotherapy; $\chi 2$ test: p >0.05.

**Table 2** Total clinical symptom score in SLIT and SCIT groups in the treatment seasons compared with a baseline

| Treatment groups | n | TCSS (Mean ± SE) | p* |
|---|---|---|---|
| SLIT | | | |
| Baseline | 25 | 11.5 ± 0.2 | - |
| 1st treatment season | 25 | 10.2 ± 0.1 | 0.05 |
| 2nd treatment season | 25 | 8.0 ± 0.2 | 0.001 |
| Endpoint | 25 | 6.8 ± 0.3 | 0.001 |
| SCIT | | | |
| Baseline | 34 | 11.8 ± 0.2 | - |
| 1st treatment season | 34 | 7.3 ± 0.2 | 0.001 |
| 2nd treatment season | 34 | 6.5 ± 0.2 | 0.001 |
| End point | 34 | 6.0 ± 0.2 | 0.001 |

SLIT = Sublingual immunotherapy; SCIT = Subcutaneous immunotherapy; TCSS = Total clinical symptom score; *Paired sample t test.

**Table 3** Medication reduction in SLIT and SCIT group

| Reduction in medication use | SLIT (n = 25) (n; %) | SCIT (n = 34) (n; %) | Total (n; %) | $\chi^2$ | p |
|---|---|---|---|---|---|
| Baseline | | | | | |
| Full treatment | 25 (100) | 34 (100%) | 59 (100) | | |
| 1st year treatment season | | | | | |
| No reduction | 2 (8.0) | 1 (2.9) | 3 (5.1) | | |
| Reduction < 50% | 17 (68.0) | 13 (38.2) | 30 (50.8) | | |
| Reduction > 50% | 6 (24.0) | 20 (58.8) | 26 (44.1) | 7.20 | 0.02 |
| Total | 25 (100) | 34 (100 %) | 59 (100) | | |
| 2nd year treatment season | | | | | |
| No reduction | 0 (0) | 0 (0.0) | 0 (0.0) | | |
| Reduction < 50% | 11 (44.0) | 17 (50.0 %) | 28 (47.5) | | |
| Reduction > 50% | 14 (56.0) | 17 (50.0) | 31 (52.5) | 0.20 | 0.62 |
| Total | 25 (100) | 34 (100 %) | 59 (100) | | |
| Endpoint | | | | | |
| No reduction | 1 (4) | 0 (0.0 %) | 1 (1.7) | | |
| Reduction < 50% | 10 (40.0) | 16 (47.0) | 26 (44.1) | | |
| Reduction > 50% | 14 (56.0) | 18 (52.9) | 32 (54.2) | 1.54 | 0.46 |
| Total | 25 (100) | 34 (100) | 59 (100) | | |

SLIT = Sublingual immunotherapy; SCIT = Subcutaneous immunotherapy.

**Table 4** Overall patient's assessment of SLIT and SCIT clinical efficacy

| Patient's assessment of clinical efficacy | Therapy | | Total | $\chi^2$ | p |
|---|---|---|---|---|---|
| | SLIT | SCIT | | | |
| Poor/mild response (n; %) | 7 (28.0) | 10 (29.4) | 17 (28.8) | - | - |
| Good/very good response (n; %) | 18 (72.0) | 24 (70.6) | 42 (71.2) | 0.14 | 0.90 |
| Total (n; %) | 25 (100.0) | 34 (100.0) | 59 (100.0) | - | - |

SLIT = Sublingual immunotherapy; SCIT = Subcutaneous immunotherapy.

Early local reactions in the SCIT group (edema and redness at the site of allergen injections, larger than 5 cm in diameter, occurring in the first 20 min.) was noticed in 14.7% of patients, while mild local reactions in the SLIT group (mouth swelling and itching) were reported by only 5 patients. There was 1 mild systemic reaction in the SCIT group, assessed as grade 2 (10), which was successfully resolved with treatment. There were no adverse systemic reactions in the SLIT group (Table 1).

## Discussion

Numerous studies (3-6, 28, 29), including our own (30), have shown that subcutaneous immunotherapy is highly effective in the treatment of allergic rhinitis and asthma, both in children and adults. However, in recent years, there has been a tremendous increase in sublingual immunotherapy, based on well documented studies with proven efficacy and safety (14-18, 23, 31-33), showing that SCIT and SLIT are similar if compared through a sufficiently rigorous study design. There is a lack of studies related to AIT in Kuwait, especially those which directly compare the efficacy of SLIT vs. SCIT with pollen allergens typical for a desert climate.

The majority of our treated patients were sensitized to either Salsola kali alone or both to Salsola kali and Bermuda grass, similar to the general distribution of sensitization in allergic population in Kuwait (34, 35, 36). Although it is generally believed that achieving good treatment adherence should be easier with SLIT, as it involves a once daily dosage at home, this was not observed in our patients (non-adherence in the SLIT group was 34.3% vs. 22.8% in the SCIT group). Relatively poor adherence to SLIT was explained by the patient's lack of knowledge about the "new vaccine", previously not used in the country. We speculated that more time may be required for patients to gain confidence in this "new treatment", which involves a relatively long duration (3 years) of self- administered vaccine at home. Additionally, non-reported, self-resolved, mild adverse reactions with SLIT in patients lost from follow up could possibly have an impact on such results. Senna et al. (37) also gave a detailed description of a uniform and consistent phenomenon of a high rate of discontinuation of SLIT within 3 years from prescription. They suggested the need for urgent investigation of this problem through closer collaboration between clinicians and manufacturers. Regardless of the many inconveniences of SCIT, especially frequent clinic visits, local discomfort at the site of injections, it seems that our patients still preferred injectable immunotherapy. Though we found a tendency for slightly better efficacy in the first year of immunotherapy in the SCIT group (statistically not significant), at the end point there was no difference between the two groups ($6.8 \pm 0.3$ in SLIT vs. $6.0 \pm 0.2$ in SCIT; $p < 0.001$) (Table 2). Such results are consistent with other studies, explaining that SLIT requires a longer period of time to reach a similar clinical effect to SCIT (38). Significant reduction in medication use (>50%) in both groups was similar during the second and third treatment years: 56% in SLIT vs. 50% in the SCIT group in the 2nd, and 56% vs. 52% in the 3rd year ($p = 0.6$, and $p = 0.4$ respectively), while in the first treatment season the reduction was significantly more in the SCIT group: 24% in SLIT vs. 58.8% in SCIT; $p < 0.02$ (Table 3). Similar to our results, Khinchi et al. (12), comparing SCIT and SLIT efficacy with a birch pollen allergen vaccine in a placebo-controlled trial, found the overall efficacy was statistically almost equal, although SCIT was slightly more effective (the reduction in symptom and medication scores was about one half in the SCIT group, in contrast to

one third in the SLIT). At the end point, we assessed the patient's personal satisfaction with immunotherapy. The results were similar in both groups. About 2/3 of patients in both groups assessed the treatment as good/very good (70.6% in SCIT and 72% in SLIT group; $p < 0.5$) (Table 4).

A positive clinical outcome in both treatment modalities was explained by sufficient length of treatment with high concentrations of well standardized allergen extracts. The long duration (at least 3 years) is an important factor in SLIT (38, 39), and likewise in SCIT. Some studies consider (38, 39) that SLIT needs a longer period of treatment to reach the first signs of good clinical outcome, in contrast to SCIT. On the contrary, Gozalo et al. (40) noticed a significant reduction in medication use soon after the first treatment year, in a group of 35 allergic patients treated with grass pollen SLIT, when compared with drug treatment alone.

There are few studies related to immunotherapy with Salsola kali (41, 42). Collas et al. (41) observed significant clinical improvement and reduction in drug consumption in patients treated with polymerized therapeutic vaccine of Salsola kali, as compared to a placebo. The Chenopodiaceous family, to which Salsola kali belongs, has been reported to be an important source of sensitization in susceptible people, not only in the Western United States and some European countries (43), but also in Iran (44 ) and in desert countries such as Saudi Arabia, UAE and Kuwait (36). It occupies the first place in the prevalence of sensitization in many countries of this region, also observed by our Centre (36), affecting more than 75% of sensitized patients. Bermuda grass is the second most common pollen allergen in Kuwait. It seems that Bermuda grass, which requires minimal watering to grow and pollinate, can survive the harsh desert climate (long and extremely hot summers, and mild and mostly dry winters). The pollination season in Kuwait is very long, starting in early March and lasting until the end of October. It is characterized by 2 constant peaks of pollination; a mild one in March-April with a predominance of grasses, and a higher peak in September-October with a predominance of Chenopodiacae (35, 36). The long pollen season, together with frequent sand storms during summer time, carrying a high number of pollen grains, increases the severity of allergic rhinitis, and frequently results in poor response to drug treatment. As a result, subcutaneous immunotherapy was introduced long ago, with a proven clinical efficacy, and recently we introduced SLIT, in order to increase safety effects and better compliance.

Local and systemic adverse reactions were analyzed separately for both SCIT and SLIT. None of our patients developed a severe adverse reaction. In the SCIT group, only one patient experienced early occurrence of a mild systemic reaction (grade 2), manifested by rhinorrhea, sneezing, and mild wheezing, without a significant fall in FEV1. The reaction occurred on maintenance dose, within first 20 minutes from injection, out of the pollen season, and was successfully managed with drugs. The frequency and severity of immediate systemic reactions in this study were similar to our previous report (30). Frew et al. (45) found similar results, reporting less than 10% of individual early systemic side effects, where most of them were nonspecific or mild (grade 1-2) in contrast to Kinchi et al. (12) who reported a few more severe systemic adverse reactions in their group of SCIT patients. In the SLIT group, no systemic reactions were reported, which contributes to the report of Wilson et al. (23), who analyzed 22 well controlled SLIT studies and found a complete absence of systemic side effects. Mild local reactions with SCIT are common, characterized by redness, swelling and discomfort at the site of injection. In

our SCIT group we found early local reaction (redness >5 cm in diameter / within 20 minutes from injection) in 14.7% cases, more frequent than in Tahimileret et al's study (20), who reported that 7.4% of the total injections in the group of 96 patients resulted in an immediate local reaction, greater than 5 cm in diameter. In all our patients, early local reactions occurred with a high dose and high concentration of allergen and in all cases this was resolved with dose reduction on their next visit. Discomfort, manifested as mild pain and swelling at the site of the allergen injection, was very common, but well tolerated by our patients, without a single request for SCIT withdrawal.

In the SLIT group, a mild self-limiting local reaction (mouth itching and swelling under the tongue) was seen in 20%, which is significantly less common than in other studies (13, 23), and they have rarely been of significance. There were no cases of dose adjustment or withdrawal due to local reaction in our SLIT group.

The overall results in this comparative study, support the clinical efficacy and safety of both treatment modalities of immunotherapy for Salsola kali and Bermuda grass pollen allergy.

Based on the limited experience of SLIT, as compared to the well-established SCIT in our allergic rhinitis patients, we found that SLIT is equally effective as SCIT. Although our results in the SLIT group showed slightly slower clinical improvement and it took a somewhat longer period of time for drug reduction, at the end point there was no difference from SCIT group. The excellent tolerability of SLIT and easy administration promotes further use of SLIT in well-motivated patients. We believe that the positive outcome in our first group of SLIT patients is a humble contribution to SLIT becoming a way to expand immunotherapy as a mode of treatment of respiratory allergy. Further studies with larger samples of subjects on SLIT are required for a final conclusion of SLIT's efficacy in allergic rhinitis patients sensitive to Salsola kali and Bermuda grass.

## Conclusion

Allergen immunotherapy, both SCIT and SLIT, is a valid treatment for patients with SAR. Both treatments are associated with significant improvement in terms of clinical efficacy and reduction in medication consumption. There were no severe systemic adverse reactions in either group. SCIT seems to be faster in action, but the end results of the two routes of administration are comparable. Convenient administration and safety of SLIT seems to make it an excellent modality of treatment in the school going pediatric population with seasonal allergic rhinitis.

**Authors' contributions:** Conception and design: NA, MA, RP, NA (authors abbreviations: 1-4); Acquisition, analysis and interpretation of data: all co-authors; Drafting the article: all co-authors; Revising it critically for important intellectual content: authors: 1-4.

**Conflict of interest:** The authors declare that they have no conflict of interest. This study was not sponsored by any external organization.

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**Citation:** Arifhodzic N, Al Ahmad M, Panicker R, Al Ahmed N, Fakim N, Mahmood F. Comparison of clinical efficacy and safety subcutaneous and sublingual immunotherapy in kuwaiti schoolchildren with seasonal allergic rhinitis. Paediatrics Today. 2012;8(1):47-57.