

Safety of Subcutaneous Specific Immunotherapy with Pollen Allergen Extracts for Respiratory Allergy

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Key Words

Allergic rhinitis · Asthma · Immunotherapy · Kuwait, pollen seasons · Seasonal allergic rhinitis · Subcutaneous specific immunotherapy, safety

Abstract

Background: Specific immunotherapy (SIT) is a well-documented treatment for respiratory allergy. However, the major risk of SIT is the development of systemic anaphylactic reactions. **Objectives:** To evaluate the safety of SIT given by subcutaneous route for 3 years to patients with seasonal allergic rhinitis (AR) with or without asthma. **Methods:** A prospective open-label study of immunotherapy (*Chenopodium album*, Bermuda grass, or both) in 181 consecutive patients with AR with or without asthma. After an initial dose-escalation phase, a maintenance dose of 0.5 ml of 100,000 PNU/ml was administered monthly for 3 years. The occurrence and severity of systemic reaction (SR) and local reaction was recorded and graded according to the WHO position paper. **Results:** Of 181 patients enrolled, 57 (31%) did not complete the study (53 due to poor compliance and 4 due to systemic side effects). All 4 patients who developed SR had asthma and all the SR occurred during the dose-escalation phase. Three patients had moderate SR (grade 2), while 1 patient had severe reaction (grade 3). Three of the SR occurred within the first 20 min after

injection and 1 SR occurred 2 h after injection. None of the reactions were life threatening and were managed easily. Total rhinitis symptom score decreased from 11.8 at baseline to 7.46 at the end of treatment ($p < 0.001$). The size of the skin prick test reaction to the main sensitising allergen was reduced from 7.48 ± 2.26 mm at baseline to 5.60 ± 2.18 mm at the end of treatment, $p < 0.01$. **Conclusion:** If a strict protocol is used, SIT is safe in AR patients with or without mild asthma and may result in significant subjective and objective improvement.

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Introduction

Specific immunotherapy (SIT) with standardized allergen extracts is the only specific treatment for type I allergy, which seems to result in modulating the immune response to the causative allergen. It is an effective treatment of allergic diseases when high-quality extracts are used [1]. The therapeutic efficacy of SIT in allergic rhinitis and asthma has been confirmed in open-label and double-blind trials, as well as in meta-analysis [2–4]. Furthermore, there are studies which have demonstrated that SIT has a long-term therapeutic effect after stopping treatment [2, 5]. Several factors are of particular importance in ensuring successful results of SIT, e.g. the appropriate selection of patients, the quality of the extract used, the

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choice of maintenance dose and longevity of the treatment [6, 7]. Meanwhile, the drawbacks of injection immunotherapy are related to the risk of inducing systemic side effects, with anaphylactic reaction being the most serious form of systemic reaction [6].

The aim of this study was to evaluate the safety of SIT given by subcutaneous route to patients with seasonal allergic rhinitis and asthma.

Methods

This prospective open-label study was conducted at the Kuwait Allergy Centre (the only referral centre for allergic problems in the country). Patients were included into the study if the following criteria were met: age 15–40 years, physician-diagnosed seasonal allergic rhinitis (AR) or allergic rhinitis and asthma for 2 or more years, sensitisation to one or more local pollen allergens, poor control of the symptoms during the previous two seasons with the use of antihistamines, local steroids and bronchodilators.

Exclusion criteria included prior treatment with SIT, presence of severe asthma and presence of other co-morbid conditions. All patients fulfilled criteria for SIT according to the WHO position paper for allergen immunotherapy [8].

The diagnosis of seasonal AR was confirmed by typical symptoms occurring during the pollen seasons in Kuwait, and asthma by the clinical symptoms and the demonstration of reversible airway obstruction. The sensitisation to specific allergens was confirmed by positive skin prick test (SPT) to relevant local pollen allergens and serum-specific IgE antibodies to those allergens (RAST class 2 or above; *Chenopodium album*, Bermuda grass, or both). SPT was performed by standardized allergen extracts (Allergopharma, Germany) in a standard manner before SIT and 3 years later. The allergens used throughout the study were obtained from the same manufacturer and applied using the same methodology. The size of the wheal was measured and the reaction was considered positive if its diameter was ≥ 3 mm than the negative control. Serum-specific IgE was determined by enzyme fluorescence assay (Pharmacia CAP System, Pharmacia Diagnostic, Uppsala, Sweden).

A standardized depot pollen allergen extract adsorbed to aluminium hydroxide (Allergopharma-Novo Helsen Depot, Germany) was used for subcutaneous immunotherapy. The activity of extracts is given in standardized quality units expressed as TU or PNU (4 concentrations: 100–100,000 PNU/ml). According to the patients' sensitisation, we used an extract of *C. album*, Bermuda grass or a mixture of both Bermuda grass and *C. album* (50/50). SIT started at the end of the pollen season (end of October 1998) and the standardized subcutaneous route was used. The protocol, suggested by the manufacturer, was slightly adapted due to the long-lasting pollen season in Kuwait. During the initial dose-escalation phase the vaccine was given twice weekly, until 0.5 ml 1,000 PNU/ml was achieved. This was followed by weekly injection until a maximum dose of the highest concentration (100,000 PNU/ml) was reached. The dose of 0.5 ml/100,000 PNU/ml was used as a maintenance dose. The injection interval was increased gradually to 4–6 weeks and continued for at least 3 years. The maintenance dose was reduced by 25% of the regular dose during the peak pollen season. The beginning of the pollen season was identified by the daily pollen counts (measured and sup-

plied by the Kuwait Air Biology Laboratory). There was a consistent seasonal variation of the pollen count during the study period [9]. The patients received their immunotherapy injection in the allergy centre after taking an antihistamine (cetirizine tablet 10 mg) as a pre-medication. They were evaluated by a physician before each injection and observed for at least 20 min after the injection.

Assessment of Side Effects

Any signs of systemic reaction were recorded. Systemic reactions were classified as early (occurring within first 20 min) and late (occurring >20 min). The reaction was graded according to the WHO position paper [8] from grade 2 to 4 (grade 2: skin symptoms, mild rhinitis and/or mild asthma symptoms; grade 3: general itching, erythema and bronchial obstruction; grade 4: severe anaphylactic reaction). The early local reaction (redness and swelling at the injection site >5 cm in diameter) was measured at 20 min after receiving the injection. Late local reaction (6 h or more) was recorded by patients and referred to the physician at the following visit.

The clinical efficacy was assessed by symptom score, and change in medications. Patients were instructed to fill in the symptoms questionnaire during the pollen season prior to SIT and annually for 3 years. A grading scale (0–3) was used for nasal/eye symptoms (sneezing, runny and itchy nose and eyes, nasal blockage, impairment of daily activities, and nocturnal bronchial obstruction (0 = no symptoms, 1 = mild, 2 = moderate, 3 = severe). Maximum total and each symptom score was 12 and 3 respectively.

The patients were allowed to use symptomatic medications if needed throughout the treatment period. The medications used by the patients during the pollen season were recorded at the beginning of the study and subsequent changes in medication were followed annually.

Statistical Methods

All analyses were done using SPSS statistical software. The ANOVA test was used to compare the difference in continuous variables (e.g. symptom scores, the size of skin reaction at baseline and at the end of treatment). The χ^2 test was used to test the difference in distribution of IgE severity classes at baseline and at the end of treatment.

Results

Of 181 patients enrolled, 57 (31%) did not complete the study (53 poor compliance, 4 systemic side effects). The remaining 124 participants (mean age 30 ± 12 years) completed the 3-year course (table 1). Of these, 70 (55%) had AR only, and 54 (45%) had both AR and asthma. The asthma patients were classified as mild intermittent 19 (35%), mild persistent 32 (59%), and moderate persistent 3 (6%) [10]. Twenty-six (20.2%) patients received *C. album* extract, 16 (12.4%) Bermuda grass extract, and 85 (67.4%) a mixture of both. A total of 5,890 injections were administered, and the rate of systemic reaction per number of injections was 0.06%, while the rate of systemic reactions per patients treated was 4/181 (2.2%). All 4 patients who developed systemic reactions had asthma,

received mixed pollen extract and developed the systemic reaction during the dose-escalation phase. Three patients had moderate systemic reaction (grade 2) while 1 had severe reaction (grade 3) (table 2). The severe reaction occurred almost immediately after injection at a dose of 0.7 ml of 10,000 PNU/ml and it was manifested with erythema, itching, general weakness and bronchial obstruction. The patient responded well to treatment and was discharged home after 2 h.

Local reaction defined as erythema and swelling >5 cm within the first 6 h after injection occurred in 15 (8.3%) patients. All the local reactions occurred later than 20 min after receiving the immunotherapy injection (table 2). To prevent further local reaction at the subsequent injections, we divided the total dose into two halves and gave half the dose into each arm. The local reaction was not a

Table 1. Clinical profile of patients who received 3-year SIT treatment with pollen allergen extract

	n	%
Male	78	61.4
Female	49	38.6
Total	127	100.0
Mean age \pm SD	30.1 \pm 12.0	
<i>Diagnosis</i>		
Rhinitis	70	55.1
Rhinitis and asthma	57	44.9
Total	127	100.0
<i>Kind of vaccine</i>		
<i>Chenopodium album</i>	26	20.2
Bermuda grass	16	12.4
Both	85	67.4

Table 2. Systemic and local reaction in patients who received 3-year SIT

	n	%
Local reaction	43	33.6
Systemic reaction	4	2.2
<i>Grades of systemic reaction</i>		
Grade 2	3	25
Grade 3	1	75
Grade 4	none	
Local reaction (within first 6 h)	15	8.3

predictor of systemic reaction as none of the 4 patients who had systemic reaction developed prior local reactions.

Total and particular symptom scores during the pollen season decreased significantly after the first year of treatment, compared to baseline, and this improvement was maintained for the duration of the study. Total symptom score decreased from 11.8 to 8.1 after the first year and 7.46 after 3 years ($p < 0.001$). Similar results were obtained with each particular symptom score (table 3). There was no significant difference in the mean daily pollen count during the allergy season (September–October) at the beginning of the study, 141 pollen/mm³, compared to the end of the study, 131 pollen/mm³.

The treatment requirements during the pollen season decreased significantly compared to baseline. At 3 years after maintenance SIT, 9 (7%) patients were not using any medications, 109 (88%) were able to reduce their medication, with only 6 (5%) requiring the same medications as baseline. None of the patients had to increase their use of medications compared to baseline. The size of the skin reaction to the main sensitising allergen decreased from

Table 3. Total and particular symptom score during pollination (before SIT) and 3 years later (mean SD)

	Before SIT	After SIT	p
Sneezing, itchy nose	2.42 \pm 0.75	1.41 \pm 0.54	<0.001
Blockage of the nose	2.55 \pm 0.65	1.46 \pm 0.64	<0.001
Cough or wheezing	1.80 \pm 0.70	1.20 \pm 0.44	<0.001
Daily activity impairment	1.45 \pm 0.56	1.26 \pm 0.49	<0.001
Total symptom score	11.8 \pm 2.62	7.46 \pm 2.11	<0.001

Table 4. Distribution of specific IgE severity classes at baseline and the end of treatment for 54 patients*

Specific IgE	IgE class at baseline	IgE class at 3 years
Class 1	none	4 (7.4%)
Class 2	3 (5.6%)	10 (18.5%)
Class 3	18 (33.3%)	23 (42.6%)
Class 4	33 (61.1%)	17 (31.5%)

* $p = 0.04$ for the difference in IgE severity class distribution at baseline compared to the end of treatment.

7.48 ± 2.26 mm at baseline to 5.60 ± 2.18 mm at the end of treatment ($p < 0.001$). Fifty-four patients had specific IgE (RAST) to the sensitising agent at baseline and at the end of the study. At baseline the majority of patients (61%) had class 4 of specific IgE, while at the end of treatment only 17 (31.5%) had the same class of specific IgE (table 4).

Discussion

Seasonal allergic rhinitis and asthma caused by sensitisation to local pollen allergens are common causes of morbidity in Kuwait [11]. The flora in Kuwait is characterised by a few families of different plants, with two pollination peaks, which are rather constant [9]. The first, smaller peak occurs in April–May related to the pollination of Bermuda grass. Flowering of local trees (e.g. *Prosopis juliflora*) comes later, lasts the whole summer, but the pollen count is much lower compared to *Chenopodium* and its role in sensitisation is less important [12, 13]. The main peak of pollination is in late summer (September–October), related to weed pollen (mostly from the family of *Chenopodiaceae*, both wild in the desert and planted in gardens). There is a very close relation between the two pollination peaks and the number of new patients with AR referred to our Allergy Centre [9, 14].

SIT is considered as a valuable mode of treatment for respiratory allergy, and use of modified allergens has improved its safety [15]. However, this form of treatment can cause undesirable side effects, among which systemic reactions are the most important. Our rates of systemic reactions, 4 patients out of 181 (2.2% per patient) and 0.06% per injection, are comparable to other reported studies. Møllerup et al. [7] and Lin et al. [16] reported a systemic reaction rate per patient of 4.4 and 2.9% respectively. The reported rate of systemic reaction per injection has been variable from 0.08% [17] to 0.5% [18]. None of the systemic reactions in our patients was life threatening. All the systemic reactions occurred in asthmatic patients during the dose-escalation phase. In 3 out of 4 patients they occurred early (within 20 min), while in 1 patient it occurred 2 h after receiving the injection. These findings are similar to those obtained in other studies [7]. These results support the recommendation of observation of the patient at a medical facility for at least 20–30 min after each injection. The fact that we used an oral antihistamine before each injection may have contributed to the low incidence of side effects. However, this needs to be verified in a randomised control study.

Our rate of local reaction of 8.3% is a little higher compared to other studies, where the local reaction rate was up to 7% [19–21]. However, our patients did not need specific treatment for the local reaction and it resolved spontaneously. Furthermore, we did not find that the local reaction was a predictor of systemic reaction, as none of our patients who had a local reaction developed a subsequent systemic reaction.

Although the assessment of clinical efficacy was not the aim of this study due to the difficulties of maintaining a control group for such a long treatment period, we tried to compare clinical symptoms in the season before and at the end of the treatment. There was significant improvement with SIT in total and particular symptoms scores. The change in SPT and specific IgE to offending allergens reflected the outcome of the symptom scores and subjective assessment of the patients.

One of the problems with long-term SIT is patient compliance. In our study, 53 out of 181 (29.2%) did not complete the study due to poor compliance. Most of these patients did not return for follow-up within the first 2 months of starting treatment. None of these non-compliant patients had any major side effects related to the SIT. The reasons for non-compliance may be related to the lack of clinical improvement early in the treatment and the longevity of treatment.

In conclusion, SIT, using alum depot-pollen allergen extracts, appeared safe and effective in a routine clinical practice. The 3-year course of treatment was associated with a low rate and mild forms of systemic reactions. Asthma was a significant risk factor for induction of systemic reaction, and asthmatics should be selected carefully for SIT.

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