Safety and Efficacy of Allergen Immunotherapy in the Treatment of Allergic Rhinitis and Asthma in Real Life

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Abstract

Background: Subcutaneous allergen immunotherapy is effective in treating allergic airway disease. Disadvantages include immediate local and systemic adverse reactions and poor compliance.

Objectives: To obtain real-life efficacy and safety data through a prospective observational study of SIT in the allergist's office.

Methods: We prospectively collected data from all patients with a diagnosis of allergic rhinitis and/or asthma and a specific immunoglobulin E-mediated sensitization to one or more aeroallergens who began SIT during the 2 year period 1 January 2005 to 31 December 2006. As part of the routine immunotherapy care patients were asked to complete a disease activity questionnaire before and yearly during the treatment. The primary outcome measure was the combined rhinitis and asthma symptoms scores. Data from patients completing at least 1 year of immunotherapy were analyzed.

Results: Altogether, 133 enrolled patients with a mean age of 22.7 years completed at least 1 year of SIT. The allergic rhinitis and asthma disease activity score decreased from a mean of 8.1 to 3.3 (rhinitis) and from 4.8 to 2.4 (asthma) on a 10 cm visual analogue scale after 1 year of SIT ($P < 0.001$ for all comparisons). Rhinitis medication use in all patients and asthma medication use in asthmatics decreased significantly. Mild local adverse reactions were almost universal. There were 11 patients (8%) who developed 14 immediate systemic, mild to moderate reactions. All reactions were successfully treated in the clinic; none required additional observation or hospitalization.

Conclusions: In the hands of experienced allergists subcutaneous allergy immunotherapy is a safe and efficacious option for patients with allergic rhinitis and asthma

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Therapeutic vaccines containing allergen extracts, otherwise known as allergen immunotherapy, are widely accepted as an efficacious treatment in allergic rhinitis [1,2], allergic asthma [1,3,4], and hymenoptera allergy [1,5]. Subcutaneous immunotherapy uses a protocol of weekly injections with gradually increasing dosages of allergen extract until a maintenance dose is achieved. Subsequently, the maintenance dose administration is reduced to biweekly and then to monthly intervals for a period of 3 to 5 years [6]. The SIT mechanism of action causes a significant decrease in Th2 cytokines and Th2 effector cell activity, increased secretion of anti-inflammatory cytokines such as interleukin-10 and tranasforming growth factor-beta and increased numbers and activity of T regulatory cells, thus diminishing the allergic reaction to specific allergens [7]. In children and young adults, additional positive outcomes of SIT are a decreased tendency for additional environmental sensitizations [8] as well as a decreased incidence of asthma in treated allergic rhinitis patients [9].

Despite the documented effectiveness of SIT in the treatment of allergic rhinitis and allergic asthma, the real-life efficacy and use of this treatment option is severely limited by perceived low patient compliance [10,11], adverse local and systemic side effects [12,13] and significant delay in effect after the initiation of therapy, all of which may translate to relatively low adherence rates.

In addition, although there is much and convincing evidence for SIT effectiveness and efficacy from international studies, few local studies have prospectively investigated the real-life efficacy in Israeli patients [14]. We undertook this prospective follow-up of patients undergoing SIT in an office setting to produce practical data of efficacy and safety of SIT for allergic patients in Israel.

Patients and Methods

Adult allergic rhinitis and asthma patients aged 18–50 years with a specific IgE-mediated sensitization to one or more aeroallergens and who began SIT during the period 1 January 2005 to 31 December 2006 were enrolled from the Outpatient Allergy Clinic of the Barzilai Medical Center. Patients were excluded if they were treated with beta-blockers, had any serious chronic underlying illness or severe uncontrolled asthma, i.e., forced expiratory volume in the first second of less than 70% of predicted values. Patients were evaluated by medical history, clinical examination and skin-prick test with common allergens. All data were collected prospectively, including information on exposure, social factors, additional diagnoses and medication usage, family history of allergic disease, exposure to house pets, active or passive smoking, measures of treatment efficacy, and patient satisfaction as well as local and systemic reactions to the SIT shots. The protocol was reviewed and approved by the Barzilai Institutional Review Board, Ashkelon, Israel.

SIT = subcutaneous allergen immunotherapy

Ig = immunoglobulin

Diagnosis of allergic rhinitis and asthma

For the diagnosis of allergic rhinitis, a symptomatic period of at least 4 weeks during the year, with at least two of the following were required: watery rhinorhea, blocked nose, itchy nose, sneezing or night cough as specified in the ARIA criteria (**a**llergic **r**hinitis and its **i**mpact of **a**sthma) for persistent rhinitis. For the diagnosis of asthma, a previous diagnosis of asthma with proof of reversibility on pulmonary function tests and response to bronchodilators was acceptable.

Skin-prick allergy testing

All tests were performed in the outpatient allergy clinic by experienced nurses using commercial allergen extracts (Hollister-Stier Laboratories LLC, USA) and a lancet-type skin-prick test device. A wheal diameter of 3 mm or more in excess of the negative control was considered a positive test result. The standard skin-prick test panel includes: house dust mite mix (D*ermatophagoides farinae* 5000 AU/ml + D*ermatophagoides pteronyssinus* 5000 AU/ml, stand.), cockroach mix (P*eriplaneta americana*, B*lattella germanica*), mixed weeds, sagebrush and Parietaria, ccat hair (standardized cat extract, F*elis catus* (*domesticus*) 10,000 BAU/ml) and dog epithelia (C*anis familiaris*), grass mix (9 grass mix, standardized), Bermuda and Johnson grass, trees (olive, pecan and cypress), and mold mix (four equal parts: Alternaria, C*ladosporium sphaerospermum*, mixed Penicillium and mixed Aspergillus).

Allergen extracts for SIT

Therapeutic vaccines containing allergen extracts were prepared using stock formulations from ALK Laboratories (Denmark). Both aqueous and glycerinated extracts were used to achieve a concentrate of 1:100 w/v of the mixed extract. In standardized extracts the stock formulation was prepared by tenfold dilutions. Separate vials were used for mites, weeds, trees and grass pollen extracts to reduce proteolytic degradation. All extracts were stored at 4°C. Therapeutic vaccine varied with each individual patient based on specific allergens identified during testing. Most patients received a variety of aeroallergens including a combination of trees, grass, weed and mites.

SIT protocol

Gradual increases in dose and concentration of vaccine content were carried out weekly for a period of 4 months. Local reaction size was measured 20 minutes after each injection. Observed large local reactions (more than 20 mm wheal size) mandated a repeat of the same dose on the next visit, while systemic allergic reactions (skin, respiratory, cardiovascular and/or gastrointestinal) required a twofold reduction in vaccine concentration. Maintenance dose was set in most cases at 0.1 ml of the stock mixed mite standardized extract and 0.5 ml of the 1:100 w/v of the pollen extracts.

Evaluation of treatment efficacy

Symptom score: We used a 10 cm visual analogue scales from 0 = absent to 10 = severe symptoms, for each symptom: general feeling, rhinorrhea, nasal congestion, nasal itching, ocular itching, sneezing, asthma symptoms (chest tightness, shortness of breath, cough) and wheezing, as recommended by the ARIA 2008 review [15] and the EPOS (European position paper on rhinosinusitis and nasal polyps, 2007) [16]. A change of 2 or more points on this scale is considered a clinically significant change with consequent significant changes in the patient's quality of life.

Medication score: As above, medication usage was recorded by patients on a VAS from 0 = no medication to 10 = repeated daily use of nasal corticosteroids, antihistamine oral medications, eyes drops, inhaler corticosteroids and beta agonists.

Patients graded their symptoms retrospectively at each visit. The use of rescue medications was recorded on the diary card in additional to regular medications.

Data collection and analysis

The results of this study are reported as ratios and/or percentages of the entire cohort. Paired samples *t*-test was used for the comparison of symptom scores before and after 1 year of SIT. Data on overall number of patient dropout from treatment were used to evaluate treatment efficacy in the intention-to-treat analysis. Systemic and local reaction rates as well as anaphylaxis rates in patients undergoing SIT in our study were compared with the reaction rates of SIT published in the literature.

Results

A total of 133 patients, of whom 104 (78%) were males, age 19–34 years (mean 22.7 years), completed at least 1 year of SIT during the study period. All had a clinical diagnosis of allergic rhinitis, 41% also fulfilled clinical criteria of bronchial asthma though only 35% had active symptoms of asthma at the time of enrollment. An overwhelming majority of patients were sensitized to house dust mites, 43% to tree pollens, 34% to grasses, 23% to weeds, 25% to cats and 8% to dog dander. A family history of allergic rhinitis was elicited in 51% and asthma in 25% of patients. A history of active smoking was elicited in 15% of our patients and passive indoor smoke exposure in 32%. Asthmatic patients had a significantly increased risk of having a family member with

Table 1. Demographic and clinical characteristics at enrollment

	All patients	AR and asthma patients	*P*
Age (yrs)	22.7	23.1	NS
Male gender (%)	78%	71%	NS
Smoker	15%	7.8%	< 0.05
Passive smoke exposure	32%	26%	NS
Family history of AR	51%	53%	NS
Family history of asthma	25%	41%	< 0.05
Sensitization to mites	98%	100%	NS
Sensitization to grass pollen	34%	33%	NS
Sensitization to tree pollen	43%	43%	NS
Sensitization to weeds	23%	24%	NS
Overall AR severity score*	8.11	8.07	NS

* On the standardized severity score, mild = 0–3, moderate = 3–7 and severe = 7–10.
AR = allergic rhinitis

VAS = Visual Analog Scale

Table 2. Symptoms score and medication usage at baseline and after 1 year of SIT in allergic rhinitis patients

	Pre-SIT VAS	1 year SIT VAS	Change VAS*	% with > 2 points* improvement	Patients with > 50% improvement	*P*
Rhinitis overall	8.11	3.32	4.79	95%	74%	< 0.001
Rhinorhea	8.03	3.00	5.03	94%	75%	< 0.001
Nasal obstruction	7.16	3.09	4.07	85%	63%	< 0.001
Sneezing	7.29	3.3	3.99	83%	62%	< 0.001
Nasal pruritus	4.50	1.99	2.50	81%	43%	< 0.001
Eye symptoms	4.73	2.08	2.64	82%	44%	< 0.001
Antihistamine use	4.89	2.18	2.71	82%	51%	< 0.001
Intranasal steroid use	3.49	1.64	1.85	80%	38%	< 0.001

* A change of 2 or more on the VAS scale represents a clinically relevant change with impact on the patient's quality of life

asthma [Table 1], and a decreased incidence of active smoking. As expected, all enrolled patients had an initial moderate to severe scoring on a standardized 10 cm VAS.

In patients completing 1 year of intervention, there was an overall improvement in the clinical allergic rhinitis symptoms score from a mean VAS of 8.1 to a mean of 3.3, i.e., an overall 59% mean reduction of the rhinitis-related symptoms score. In addition, statistically significant improvements were observed in all individual symptoms scores as well as medication usage scores [Table 2]. Altogether, 100 patients (75%) had more than a 50% improvement on their rhinitis symptoms score compared to their initial evaluations; 87% of patients had an improvement of more than 2 severity points in their rhinitis-related VAS scores after 1 year of treatment. On the standardized 10 cm VAS for the assessment of rhinitis, a difference of 2 points is considered clinically significant of a change with true impact on the patient's quality of life [16].

Patients with allergic rhinitis and active asthma at the time of enrollment (N=44) showed a significant improvement in their overall asthma disease activity score from a mean of 4.8 to 2.4 ($P < 0.001$), as well as in individual asthma-related symptoms scores and asthma inhaler medication usage [Table 3]. Furthermore, 39% of patients had more than a 50% improvement on their asthma-related symptoms score compared to their initial evaluations. Seventy percent of patients had an improvement of more than 2 severity points in their asthma-related VAS scores after 1 year of treatment.

Twenty-four individuals who began SIT during the study period did not complete 1 year of therapy and therefore are considered treatment dropouts. In most cases this was due to logistical barriers, work schedule or travel distance to the clinic. In the intention-to-treat analysis therefore, at the end of 1 year of SIT, 100 patients out of 157 starting therapy (64%) had a more than 50% reduction in their allergic rhinitis symptoms score while 74% had a significant improvement in rhinitis-related VAS scores.

Eleven patients (8%) were diagnosed with 14 immediate systemic reactions, ranging from generalized skin rash (grade 1) to mild or moderate respiratory involvement (grade 2). All reactions were successfully treated in the clinic, and none required additional observation or hospitalization.

Table 3. Symptoms score and medication usage at baseline and after 1 year of SIT in patients with allergic rhinitis and asthma

	Pre-SIT VAS	1 year SIT VAS	Change VAS*	% with > 2 points improvement	% with > 50% improvement	*P*
Rhinitis overall	8.07	3.28	4.78	95%	68%	< 0.001
Asthma overall	5.70	2.80	2.89	70%	49%	< 0.001
Rhinorhea	7.78	3.15	4.63	93%	66%	< 0.001
Nasal obstruction	7.11	3.00	4.11	88%	60%	< 0.001
Sneezing	7.52	3.46	4.07	86%	62%	< 0.001
Nasal pruritus	4.04	1.63	2.41	76%	43%	< 0.001
Eye symptoms	5.11	2.24	2.87	77%	45%	< 0.001
Antihistamine use	5.13	2.33	2.80	80%	51%	< 0.001
Asthma inhaler use	4.35	1.52	2.83	73%	58%	<0.001

* A change of 2 or more on the VAS scale represents a clinically relevant change with impact on the patient's quality of life

Discussion

Therapeutic vaccines containing allergen extracts are an effective and safe procedure that has been shown to significantly improve symptoms associated with allergic disease. The purpose of this study was to investigate, through a prospective meticulous record of real-life SIT data, whether SIT is a safe and efficacious treatment in daily real-life practice in the local allergist's office.

The results confirm the real-life efficacy and safety of SIT in our local patient population. The reported adverse systemic events, 14 reactions in 11 patients (8% of the treated population), with a calculated approximate reaction rate of 16/1000 office visits or 4/1000 allergy shots, is comparable to previously reported local [12,13] and international studies [17,18]. None of the reactions required continued observation or hospitalization or necessitated the interruption of SIT.

An overall 74% efficacy at 1 year of treatment in the intention-to-treat analysis, with a mean reduction of 59% in the mean rhinitis-related symptoms score, though seemingly suboptimal, needs to be compared with the real-life results after 1 year of other recommended interventions in allergic rhinitis. Very few non-immunotherapy interventional studies have continued to follow patients for 52 weeks. One study looking at 1 year results after surgical intervention in severe perennial rhinitis showed that only 38% of patients were "satisfied" with the results of surgery, irrespective of their atopic status [19]. In one of the few studies following the long-term individual allergic rhinitis-related symptoms score improvement with antihistamines in an intention-to-treat analysis, Bachert et al. [20] showed that only 76.4% of patients remained in the study (necessitating just an oral home medication without injections and supported by a study team coordinator and funding) at the 6 month follow-up, and overall only a mean improvement of 39% from baseline symptoms score was measured. In a study evaluating 1 year safety and efficacy of fluticasone propionate aqueous nasal spray in patients with perennial allergic rhinitis, Holm and co-authors [21] reported the results in 29 patients remaining in the study, out of 42 initially enrolled (only 69%). Compared to placebo, there was a significant reduction in symptoms score though the

magnitude of reduction is not detailed and the symptom score evaluation was not standardized.

The results of SIT in reducing asthma-related symptoms score and medication usage in patients with allergic rhinitis and asthma, although statistically and clinically significant, show a smaller magnitude of effect compared to the results in allergic rhinitis. This is similar to published international studies and may be due to the more severe and 'stubborn' phenotype associated with asthma complicated by allergic rhinitis [15].

Overall, patient compliance with "real life" SIT in our hands is as good as or better than general compliance with treatment of these conditions, and immediate efficacy was comparable to or better than other therapeutic options where these results are available long term. In addition, it is important to remember that SIT is the only treatment with long-term effects on both the immune system and the potential for influencing the natural course of disease. Whereas all studies trying to 'prevent' asthma through long-term treatment with anti-inflammatory medications such as inhaled steroids in children have failed in their goal [22,23], immunotherapy has been shown to decrease/prevent the development of additional sensitizations [24] as well as the development of asthma in patients with allergis rhinitis [9,25].

The limitations of this study are its relative small size and short follow-up period. Additional long-term benefits such as reduced sensitizations and decreased incidence of asthma could not be evaluated. Larger, multicenter, real-life studies comparing SIT with other therapeutic options are needed. In addition, standardized questionnaires for the assessment of quality of life were not used in this real-life study, mainly because of the time limitations of a working office environment. We suggest an attempt to develop simpler tools for the assessment of quality of life in allergic patients, such as a validated VAS score, which would be of great use in real-life settings.

Conclusions

In the hands of experienced and well-trained allergists, subcutaneous immunotherapy is a safe and efficacious option for patients with allergic rhinitis and asthma. In addition to the immediate benefits, reasonable safety and compliance, SIT is the only treatment with potentially beneficial long-term effects in the prevention of asthma.

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