

Twenty years' observation of subcutaneous pollen allergoid immunotherapy efficacy in adults

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Abstract

Introduction: It is valuable to determine the long-term efficacy of allergen-specific immunotherapy (SIT) and whether it can cure allergy.

Aim: For this study, patients were prospectively observed for 20 years after completion of SIT to determine its effectiveness.

Material and methods: A total of 1006 patients who underwent SIT for pollen allergy were observed for 20 years to assess the efficacy of SIT. The rhinitis symptom score (RSS) and asthma symptom score (ASS) were measured after SIT completion. The possibility of allergy cure was estimated based on three sets of criteria: group A – neither symptoms nor intake of medication during the analysis period, group B – no symptoms during the analysis period (but possible medication intake), and group C – at most one mild symptom during the analysis period.

Results: After SIT, approximately 25% of patients showed complete relief of allergy symptoms and had no need for symptomatic drug treatment during the pollen season. The level of effectiveness of SIT was similar throughout the treatment period. During the observation period after SIT, RSS ranged from 1.51 to 1.82, and ASS ranged from 1.22 to 1.29. The treatment effect at 10 and 20 years after SIT was comparable, regardless of whether criterion A or B was used. However, the effect of SIT using criterion C was lower than those using criteria A and B for the analyzed time points.

Conclusions: For this study cohort, SIT had a long-term effect that did not depend significantly on the duration of immunotherapy against pollen.

Key words: immunotherapy, allergic rhinitis, IgE, grass.

Introduction

Allergen-specific immunotherapy (SIT) is the repeated administration of allergen products to induce clinical and immunologic tolerance to the offending allergens. Allergen-specific immunotherapy is the only etiology-based treatment that has the potential for disease modification. This is reflected by long-term remission following SIT discontinuation and possible prevention of disease progression and sensitization to new allergens [1–5]. Allergen-specific immunotherapy is considered the only treatment with the ability to cure allergy by modulating the immune system. Previous studies have evaluated the effect of SIT for up to 3–5 years after immunotherapy discontinuation, but few have evaluated its efficacy in the long term [6–8].

The long-term effectiveness of SIT suggests that it may actually cure allergy; however, clear criteria for such an effect are lacking. Tribanek *et al.* proposed the following principles to assess the absence of allergy symptoms or allergy cure [9].

Group/criterion A – neither symptoms nor intake of medication during the analysis period. Group/criterion B – no symptoms during the analysis period (but possible medication intake). Group/criterion C – at most one mild symptom during the analysis period [9].

For this study, patients were prospectively observed for 20 years after SIT to determine the effectiveness of treatment according to the criteria for allergy cure.

Aim

For comparison, a control group of allergic patients who did not receive SIT was included in the study.

Material and methods

Patients

A total of 1136 patients pre-qualified for this study based on the following inclusion criteria: pollen allergy

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with allergic rhinitis and/or asthma and the completion of at least a 3-year course of SIT to the allergens. A total of 105 patients were lost to follow-up during the 20 years of prospective observation. Finally, 1006 patients (501 women and 505 men) were included in the study. The mean age of the study group at the start of the prospective observation (after completion of SIT) and at the end of the study was 25.1 ±9.2 and 46.6 ±8.9 years, respectively.

The patients were divided into the following sub-groups:

I – Patients with seasonal allergic rhinitis (SAR) and bronchial asthma due to monosensitization to grasses and cereals (grass pollen allergy) who received a minimum of 3 years of preseasonal immunotherapy with Allergovit (composition: 015 grasses/cereals – 100%; Allergopharma, Reinbek, Germany).

II – Patients with SAR and/or bronchial asthma due to monosensitization to trees who received a minimum of 3 years of preseasonal immunotherapy with Allergovit (composition: 108 Birch – 35%, 115 Alder – 30%, 129 Hazel – 35%, Allergopharma, Reinbek, Germany).

III – Patients with SAR and/or bronchial asthma due to monosensitization to mugwort who received a minimum of 3 years of preseasonal immunotherapy with Allergovit (composition: 106 Mugwort – 100%, Allergopharma, Reinbek, Germany).

0 – Control group of patients with SAR and/or bronchial asthma due to pollen allergy who only received symptomatic treatment, not SIT.

Detailed information is presented in Table 1.

The inclusion criteria for the control group were as follows: comparable duration of pollen allergy to that of the study group at the start of prospective observation, only 3–5 years of symptomatic therapy without SIT dur-

ing the same time period as immunotherapy administration in the study group. The mean age of the control group at the start of observation was 19.7 ±6.3 years.

All patients were subjected to the following procedures: retrospective analysis of diagnostic procedure results (history of allergy, skin prick test and specific IgE) and assessment of the cumulative dose of Allergovit over the entire course of SIT, all of which were performed between 1985 and 1992.

The mean duration of prospective observation after SIT was 20.2 ±1.1 years, and the following procedures were performed between 1992 and 2012:

– Each patient’s allergy symptoms were monitored during pollen season (February-August) prior to SIT administration, 1 year after SIT and in the tenth and twentieth year after SIT. When necessary, patients were allowed to use the following drugs: antihistamine (levocetirizine, 5 mg tablets), intranasal corticosteroid (mometasone), topical ocular antihistamine drops (ebastine) and methylprednisolone (4 mg tablets). Other anti-allergic drugs were not permitted during the study. The nasal corticosteroid was the first-line treatment. The patients were instructed to record their use of the above medications on a diary card, and a specific weekly score was assigned (1 point: use of only nasal corticosteroid or eye drops at a minimum of one per week; 2 points: the previous therapy plus one tablet of levocetirizine at a minimum of one per day; 3 points: both previous therapies plus one 4 mg tablet of methylprednisolone at a minimum of one per day). The clinical evaluation included the use of numerical scores: 4 items of the “rhinitis symptom score” (RSS) (sneezing, rhinorrhea, nasal itch and obstruction) and 4 items of the “asthma symptom score” (ASS) (wheezing, dyspnea, cough and exercise-induced asthma) were evaluated with a rank-

Table 1. Characteristics of analyzed patients at the beginning of the observation period

Characteristics	Group I	Group II	Group III	Group 0	P-value
Number (%)	370	342	394*	–	
	1006 (B + C + D)			967	NS
Mean age at the end of the study		46.6 ±8.9		45.1 ±11.3	NS
Female, n (%)		501 (49.8)		471 (48.7)	NS
SAR, n (%)		990 (98.4)		788 (81.5)	NS
SAR and asthma, n (%)		211 (21)		179 (18.5)	NS
Mean duration of the disease at the start of SIT		2.8 ±1.9		–	–
Mean weekly rhinitis symptom score (RSS) at the start of SIT		5.81 ±1.95		5.37 ±1.34	0.187
Mean weekly asthmatic symptom score (ASS) at the start of SIT		4.83 ±0.85		4.19 ±0.568	0.177
Mean weekly medication score at the start of SIT		1.877 ±0.129		1.912 ±0.201	0.543
Mean duration of SIT [years]		3.8 ±1.4		–	
Mean cumulative dose of SIT TU	15463* ±1201	14112* ±1750	14510* ±1444	–	–

*Cumulative dose of the allergen in TU (therapeutic units), SAR – seasonal allergic rhinitis.

ing scale from 0 (= no symptoms) to 3 (= severe symptoms) (max score = 12), according to the ARIA and GINA guidelines [10, 11].

– All patients with asthma were diagnosed based on the ECRHS II questionnaire [12], physical examination and spirometry with a positive reversibility test (Lungtest 1000, MES, Krakow, Poland). A positive reversibility test result was defined as an increase in the forced expiratory volume in 1 s (FEV_1) of $\geq 12\%$ or 200 ml from baseline, which is in accordance with the criteria of the ATS and ERS [13]. For 8 and 48 h prior to testing, the patients were restricted from using short-acting β_2 agonists and long-acting β_2 agonists, respectively. Current smokers refrained from smoking for 1 h before testing. Testing was delayed for 4 weeks for patients who presented with a respiratory tract infection. Asthma severity and disease control were determined based on the patient history and spirometry and were assessed according to the criteria of the Global Initiative for Asthma (GINA) [10].

Visits were performed once a year at the outpatient allergy clinic during the observation period; however only 3 time points were included in the analysis.

This study was approved by the Bioethical Committee of the District Medical Board of Silesia in Katowice, Poland (NN-2456/92).

Results

A total of 1006 SIT patients and 954 controls completed the entire observation period. The effectiveness of SIT according to the Tribanek criteria at the end of SIT and at the tenth and twentieth year after SIT are shown in Figure 1 [9].

The treatment effect at 10 and 20 years after SIT was comparable, regardless of whether criterion A or B was used. However, the effect of SIT using criterion C was lower than those using criteria A and B for the analyzed time points.

There was no significant difference in SIT efficacy between the subgroups of patients with immunotherapy to different allergens. Among the patients who did not receive SIT (group 0), none met criterion A for allergy cure, and only 3% and 8% met criteria B and C, respectively. Over the 20 years of observation, there was no significant change in this trend.

Assessment of nasal symptoms by the rhinitis symptom score (RSS)

Rhinitis symptom score (RSS) (mean \pm SD) was maintained at a low level immediately after completion of SIT and at the tenth year after SIT; however, it was slightly but significantly increased at the twentieth year after SIT. The following mean RSS values were obtained:

- baseline pollen season after SIT: 1.51 ± 1.11 ,
- tenth year after SIT: 1.68 ± 1.86 ($p > 0.05$ vs. baseline),

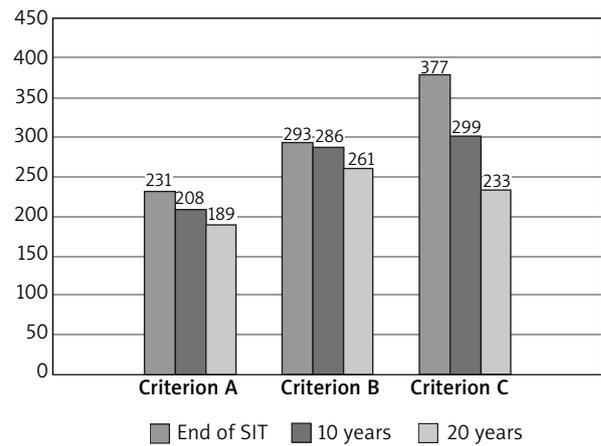


Figure 1. Effectiveness of SIT at the 10th and 20th year after treatment termination according to Tribanek criteria

– twentieth year after SIT: 1.82 ± 1.06 ($p < 0.05$ vs. baseline).

For the control group (no SIT), RSS did not change significantly during the observation period, with a mean value of 4.78 ± 2.89 .

Assessment of asthmatic symptoms by the asthma symptom score

Asthma symptom score (ASS) was low after SIT and did not change significantly during the observation period (as described previously):

- baseline pollen season after SIT: 1.22 ± 1.04 ,
- tenth year after SIT: 1.27 ± 0.97 ($p > 0.05$ vs. baseline),
- twentieth year after SIT: 1.29 ± 0.86 ($p > 0.05$ vs. baseline).

For the control group (no SIT), ASS did not change significantly during the observation period (5.03 ± 3.11).

Medication score

The mean weekly medication scores during the pollen season after SIT and at the tenth and twentieth year after SIT were similar, with all values being low and not significantly different: 0.422 ± 0.186 vs. 0.441 ± 0.223 vs. 0.469 ± 0.226 , respectively. The medication score was significantly lower in the SIT group than in the control group ($p < 0.05$), with a fairly constant value in the control group of 1.937 ± 1.061 throughout the observation period.

Differences in RSS and ASS between patients receiving 3 and 5 years of SIT

There were no significant differences in RSS or ASS between patients who received 3 and 5 years of SIT (Figure 2) or between the subgroups of patients in the SIT group with immunotherapy to different allergens.

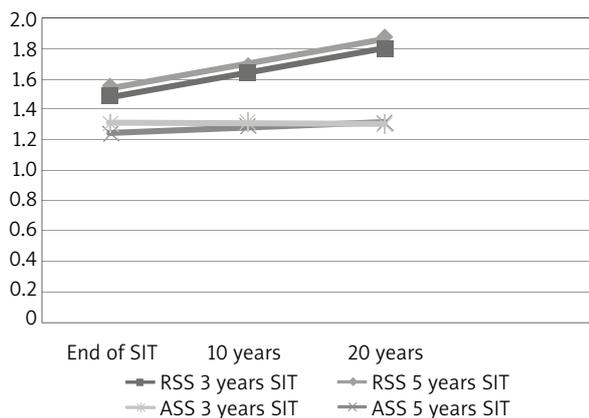


Figure 2. Effectiveness of 3 and 5 years of SIT in terms of RSS and ASS

Discussion

Allergen-specific immunotherapy has disease-modifying effects. The administration of allergen extracts activates allergen-specific blocking antibodies, tolerance-inducing cells and immune mediators, which prevent further exacerbation of the allergen-triggered immune response, block the specific immune response to the allergen and attenuate the inflammatory response to the allergen in tissues. Numerous trials in adults and a few trials in children and adolescents have generated strong evidence of the efficacy of SIT for the treatment of pollen allergy-induced allergic rhinoconjunctivitis. From a long-term perspective, SIT is considered significantly more cost-effective for the treatment of allergic rhinitis and allergic asthma than pharmacotherapy, and SIT has a prolonged effect after therapy completion. However, the efficacy of SIT is heavily dependent on patient compliance.

This is the first long-term study of SIT for pollen allergy in adults to show efficacy of 10–20 years following therapy completion. The results showed that SIT efficacy persists at a nearly constant and good level for 20 years after SIT completion. This is particularly evident in regards to improvement in asthmatic symptoms. The observation of long-term efficacy of SIT is unique to this study. Eng *et al.* conducted a similar prolonged study and observed prolonged efficacy of preseasonal grass pollen immunotherapy in children [14]. That finding corresponds with those of other studies; however, all such studies had a shorter observation period (3–12 years) than the current study [7, 8, 15]. Similarly to previous studies, we found that a 3-year course of immunotherapy is sufficient to provide acceptable efficacy [15, 16]. Extending the immunotherapy course to 5 years does not significantly alter the effects of the treatment [15]; however, conflicting data have been published [15, 17].

In the current study, SIT provided sustained long-term asthma symptom reduction. This finding is of particular importance because it indicates that SIT has high and

sustained efficacy in the treatment of asthma. Jacobsen *et al.* found that specific immunotherapy has long-term clinical effects and the potential to prevent the development of asthma in children with allergic rhinitis up to 7 years after treatment termination [18]. It appears that the prolonged effect of SIT is independent of the type of allergen administered. Previous studies had similar results to those of this study in terms of the disease-modifying effects of immunotherapy [5, 7, 19, 20]; however, this requires further investigation.

A limitation of this study was that it did not use a randomized, double-blind, placebo-controlled protocol. This was impossible due to the retrospective portion of the research, which included determination of patient diagnosis and desensitization. However, the control group, which was not desensitized for various reasons, such as lack of consent, and contraindications for SIT, generated data that confirmed the lack of a long-term effect of symptomatic treatment. A few patients in the control group showed a significant reduction in symptoms at the 20-year follow-up time and we hypothesize that this was due to natural and spontaneous allergy remission.

Using the strictest Tribanek criterion (A), SIT cured allergy in 20–30% of patients in this study, which is consistent with the observations of Tribanek *et al.* [9]. A new observation of this study was the sustained effect of SIT at a nearly consistent and good level for 20 years. A slightly lower rate of cured allergy was observed for patients that met the B or C Tribanek criterion. Curing allergy is still a major clinical challenge, but only one other study has focused on that issue [9]. This is probably because a standard definition of “curing allergy” does not exist. Tribanek *et al.* defined “curing allergy” according to the provisions in the guideline on the Development of Products for Specific Immunotherapy [9]. They used follow-up data from a double-blind, placebo-controlled trial investigating SCIT with a grass pollen allergoid, and the results were similar to those of our study. Similar trials that investigate desensitization of patients to other allergens and other routes of SIT administration are necessary to clarify this phenomenon. Novel strategies to minimize the side-effects and improve the efficacy of immunotherapy are of considerable interest in the treatment of atopic diseases. Promising animal and human studies of various treatment approaches, such as peptide immunotherapy, DNA vaccination, CpG oligonucleotides and mycobacterial vaccines, showed that it may be possible to prevent or cure atopic diseases in the future. The SIT should be recognized not only as the first-line therapeutic treatment for allergic rhinoconjunctivitis but also as a secondary preventive treatment for respiratory allergic diseases.

Conclusions

Our findings confirmed a prolonged clinical effect of SIT after treatment termination. During the 20-year

observation period after SIT, a permanent effect was observed regardless of the therapy duration or type of pollen allergen administered.

Conflict of interest

The authors declare no conflict of interest.

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