

Long-term efficacy of injected allergen immunotherapy for treatment of grass pollen allergy in elderly patients with allergic rhinitis

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ABSTRACT

Background: The effect of prolonged allergen immunotherapy is still insufficiently known, especially in elderly patients.

Objective: The effect after a 3-year course of injected allergen-specific immunotherapy (AIT) for grass pollen allergy in elderly patients with allergic rhinitis was observed.

Methods: Thirty-eight elderly patients (mean $\pm$ standard deviation, 66.2 $\pm$ 2.7 years old) who received preseasonal injected AIT or placebo for grass pollen allergy were monitored for 3 years and compared with a placebo group. The combined symptom medication score (CSMS), serum level of immunoglobulin G4 (IgG4) to *Phleum pratense* 5 (Phl p5) and quality of life were assessed immediately after AIT and 3 years later.

Results: After AIT, the CSMS was significantly decreased from 2.15 (range, 1.27–3.00) to 1.13 (range, 0.79–1.36) ($p=0.03$) and remained lower (1.41 $\pm$ 0.72 versus 2.41 $\pm$ 1.11) than that in the placebo group during the 3 years after AIT. Serum-specific IgG4 against increased during the course of AIT and remained at a high level during further observation. Quality of life, based on the Rhinoconjunctivitis Quality of Life Questionnaire, was significantly decreased in the patients who received AIT from 1.51 (95% confidence interval [CI], 1.21–1.84) to 1.01 (95% CI, 0.93–1.87) ($p<0.05$) and was decreased to 0.97–1.26 (95% CI, 0.88–1.82) during the 3 years after discontinuation of AIT.

Conclusion: A prolonged positive effect after AIT for grass pollen allergy was observed in elderly patients with allergic rhinitis. Further trials are needed to confirm this effect.

Clinical trial MC56871/12, www.clinicaltrials.gov.

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Allergen-specific immunotherapy (AIT) is a highly effective therapy for allergic rhinitis, and it is widely used according to present guidelines.^{1,2} There are many studies and meta-analyses that prove the effectiveness and safety of AIT in different age groups, including elderly patients with allergic rhinitis.^{3,4} There are many ways to assess the effectiveness of AIT, such as the symptom medication score, different variations of similar indicators, and immunologic parameters (e.g., specific immunoglobulin G4 [sIgG4], sIgE, and exposure assessment in provocation chambers).⁵ The effect of AIT should be achieved in the first year of treatment and, finally, assessed after 3 years of treatment.¹

Does AIT provide a sustained clinical and immunologic effect after treatment is discontinued? This is an important question, and long-term treatment efficacy has been defined by the European Academy of

Allergy and Clinical Immunology (EAACI) as a sustained clinical benefit that lasts for at least 1 year after discontinuation of immunotherapy.² More studies aimed to assess this long-term effect by having relatively small control observations that analyzed the prolonged effect of AIT for 1 or 2 years after discontinuation of treatment.³ The aim of this study was to investigate the sustained effect in a 6-year double-blind, placebo controlled trial, which included 3 years of blinded follow-up after completion of a 3-year treatment period with Purethal Grasses (Hal Allergy, Leiden, Netherlands) or placebo.

The primary outcomes were changes in the mean total combined symptom medication score (CSMS) in the grass pollen season, which was assessed in a *post hoc* analysis during AIT and after AIT during follow-up in comparison with placebo. The CSMS is based on the sum of the total daily symptom score (dSS) and total daily medication score (dMS). The secondary outcomes were the assessment of the effect of sustained AIT on quality of life with the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) and free days of symptoms during the exposure season. In addition, the following immunologic parameters were monitored: sIgE and sIgG4 to *Phleum pratense* and the sIgE/sIgG4 ratio to *P. pratense* as well as

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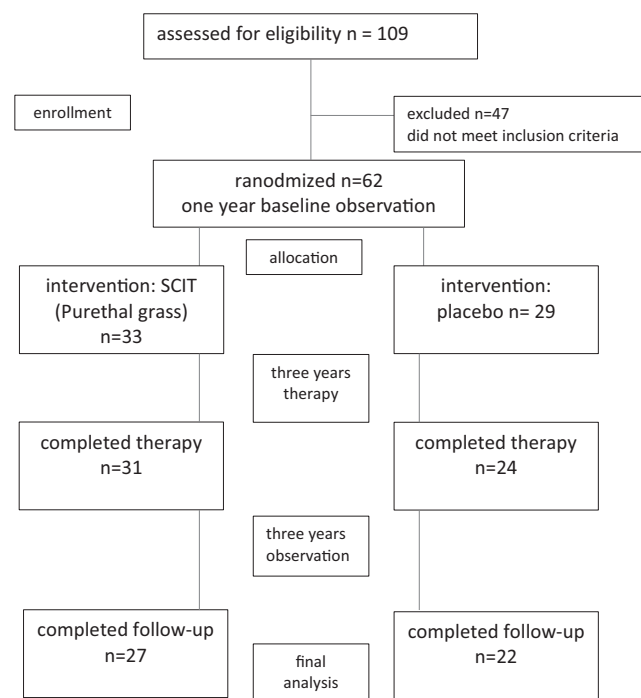


Figure 1. Number of participants assessed for eligibility that completed the study.

reduction of nasal response during allergen provocation with grass.

METHODS

Study Design

This trial was a prospective follow-up observation of patients with allergic rhinitis who completed 3 years of preseasonal AIT in a randomized, double-blind, placebo controlled trial.⁶ During a further 3-year follow-up observation, the patients who received AIT were compared with those who received placebo (Fig. 1). The study was approved by the local ethics committees of the Medical University of Silesia in Poland AC (34211/2011). All the patients signed an informed consent form.

Patients

A total of 109 patients, ranging from 65 to 75 years of age, were recruited from the outpatient allergy clinic to assess their eligibility for inclusion in the study. The detailed process of screening was described in a separate study.⁶ The inclusion criteria were moderate or severe intermittent allergic rhinitis according to the Allergic Rhinitis and its Impact on Asthma guidelines.⁷ Additional inclusion criteria were a positive skin-prick test (SPT) result to grass pollen, a concentration of sIgE against *P. pratense* of >0.75 kU/L, and positive nasal provocation tests (NPT) results with grass pollen

mixture allergens. The exclusion criteria were clinical allergy and/or positive SPT and sIgE results to other inhalant allergens (including other pollens), a diagnosis of bronchial asthma, nonallergic rhinitis (especially senile or vasomotor rhinitis), and severe nonstable diseases. However, patients with stable coronary disease, diabetes, and arterial hypertension were permitted in the study.

Procedures

SPTs. SPTs were performed by using inhalant allergens (HAL Allergy B.V, Leiden, Netherlands) from the following panel: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, mixed 5 grasses (*P. pratense*, *Dactylis glomerata*, *Anthoxanthum odoratum*, *Lolium perenne*, and *Poa pratensis*), mixed tree, mugwort, *Alternaria*, *Cladosporium*, and dog and cat allergens. Positive (10 mg/mL of histamine) and negative (saline solution) controls were also included. A grass pollen allergy was defined as a positive SPT result for five grass pollen allergens, with a minimum wheal diameter of >3 mm than the negative control.⁸ Serum sIgE reactivity to the grass pollen allergen mixture was determined by using ImmunoCAP (ThermoFisher Scientific, Uppsala, Sweden) tests. The results were considered positive when the sIgE concentration was > 0.35 IU/mL (according to the manufacturer's instructions).

NPTs. NPTs were conducted by using acoustic rhinometry (GM Instrumental, ProVita, Poland) with commercial grass pollen mixture allergens. The concentrations were 100 AU/mL, 1000 AU/mL, and 10,000 AU/mL, and the mixture was delivered as one puff per nostril by using the method described by Bachert *et al.*⁹ and Dordal *et al.*¹⁰ A reduction in the peak nasal inspiratory flow of $\geq 40\%$ and an increase in symptoms of ≥ 5 points were considered to be positive NPT criteria, as defined by Bachert *et al.*⁹ and Dordal *et al.*¹⁰ The NPTs were repeated after 3 years of treatment and during the subsequent 3 years of follow-up (between October and November).

Treatment Phase

The study protocol was published by Bozek *et al.*, authors after the first treatment phase.⁶ In brief, 60 patients were individually randomized in comparable numbers to one of two "parallel" groups by using a double-blind method (Fig. 1). The randomization procedure with random selection relied on the use of computer-generated numbers with the use of a computer program (Excel, version 14.2.0, 2011; Microsoft Corp, Warsaw, Poland). Thirty-one subjects in the AIT group and 24 subjects in the placebo group completed the 3-year observation period. The groups

Table 1 Characteristics of patients before randomization

	Active Group	Placebo Group	<i>p</i>
Randomized patients, <i>n</i>	33	29	
Age, y	66.2 ± 2.7	67.5 ± 1.8	0.38
Female, <i>n</i> (%)	19 (57)	17 (59)	0.47
Duration of rhinitis, y	9.1 ± 6.7	6.9 ± 3.9	0.39
smokers, <i>n</i>	4	3	0.62
Mean CSMS (baseline)	2.15 ± 1.07	2.31 ± 1.19	0.21
Total IgE, kU/L	211 ± 69	198 ± 88	0.34
Specific IgE Phl p 5	12.09 ± 6.04	11.21 ± 5.16	0.19
Mean symptoms score after NPT to grass pollen	6.4 ± 2.32	5.86 ± 3.12	0.62
Mean nasal flow decrease after NPT to grass pollen, %*	78.4	82.4	0.39

CSMS = Combined symptoms medication score; IgE = serum concentration of immunoglobulin E; NPT = nasal provocation test.

*With allergen concentration: 10,000 AU/mL.

were comparable at baseline (Table 1). The patients were randomly selected to receive Purethal Grasses 20,000 AUM/mL (pollen mixture extract solution of *Agrostis stolonifera*, *A. odoratum*, *Arrhenatherum elatius*, *D. glomerata*, *Festuca rubra*, *Holcus lanatus*, *L. perenne*, *P. pratense*, *P. pratensis*, *Secale cereal*, and *Loe edasi* (HAL Allergy B.V.) or a placebo.

Purethal Grasses were administered as preseasonal therapy (January–April) by using the following regimen: one dose, 0.1 mL; two doses, 0.2 mL; and three doses, 0.4 mL every week; and four to seven doses of 0.5 mL of Phl p5 (26.3 µg/mL) every 2 weeks. It was repeated for 3 consecutive years. By using this schedule, the average cumulative dose was 460,500 bioequivalent allergy units, which comprised ~690 µg of Phl p5 administered to each patient who underwent active treatment for all 3 years of the study. The baseline was performed as one season of follow-up visits without treatment, and then 3 years of AIT or placebo treatment. The placebo was administered in the same protocol as were the Purethal Grasses.

Diary

Combined Symptom Medication Score. CSMS was calculated as a mean weekly score by each patient during the grass pollen season: baseline; 3 years after AIT or placebo; and the first, second, and third year after AIT/placebo was discontinued. The grass pollen season lasted from May until August. The CSMS was based on the equal weight of the dSS and dMS. The dSS scored nasal (itchy nose, sneezing, runny nose, blocked nose) and conjunctival symptoms (itchy red eyes, watery eyes). For each symptom, 0–3 points were applied (0, no symptoms; 1, mild symptoms; 2, moderate symptoms; and 3, severe symptoms). In the total daily dSS, all obtained points were divided by six

analyzed symptoms. The maximum daily score was 3. The dMS had the following scoring: 1 point for antihistamine use, 2 points for intranasal corticosteroids, and 3 points for oral corticosteroids. In this way, the maximum score was 3. The mean weekly result of the CSMS for each patient was used in further analyses. Free days were defined as the day before medical use and without any symptoms (CSMS = 0).

Quality of Life

The RQLQ was checked in each patient at baseline, after AIT or placebo treatment and during 3 years of follow-up after discontinuation of therapy. It was always performed after the grass season (September–October).

sIgE and sIgG4 Measurements

The serum concentrations of sIgE and sIgG4 against Phl p 5 were determined in the blood serum by using enzyme-linked immunosorbent assay tests by ImmunoCAP (ThermoFisher Scientific, Uppsala, Sweden) before and after 6 years of observation.¹¹

Pollen Counts

The local grass pollen counts from May to August were determined by using a volumetric pollen trap (Burkard, Scientific Ltd, Uxbridge, U.K.). The data are presented in Fig. 2. The grass pollen season was defined as 4 months, from May to August, when the grass grains are detected in the air in Poland.

Statistics

The statistical analysis was performed by using Statistica version 8.12 (SoftPol, Cracow, Poland). The intention-to-treat (ITT) analysis, which included all randomized patients, was performed. The modified

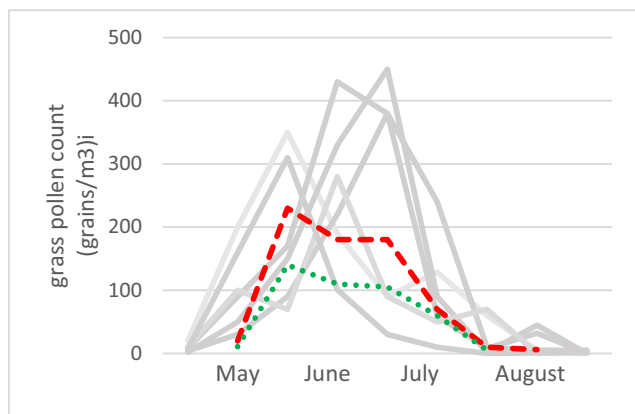


Figure 2. Grass grains counts and the average of CSMS recorded by patients in the active group during the first and last pollen seasons of observation. The gray lines indicate subsequent pollen seasons during the 6 years of the study; the red line indicates the mean of the CSMS baseline in the active group; the green line indicates CSMS 3 years after the end of allergen immunotherapy (AIT) in the active group. CSMS = Combined Symptom Medication Score.

ITT (mITT) population included all randomized participants with evaluable end points (therapy and follow-up). Nonparametric tests were used because the data were not normally distributed. The Wilcoxon test was used to analyze differences between the groups. The χ^2 test was used to analyze the differences between the NPT flow and the rate of adverse events in each study group. The analysis of variance test was used to analyze the symptom medication scores. Differences were considered significant at $p < 0.05$.

RESULTS

The participant numbers after enrollment, randomization, treatment, and follow-up are presented in Fig. 1. The basic characteristics for each group are presented in Table 1. A total of 62 participants (ITT population) were enrolled, and 55 (88.7%) completed the primary end point evaluation at 3 years. In all, 29 subjects in the AIT group and 22 subjects in the placebo group completed the 3-year further observation period (mITT population). Adherence to injection was recorded by the staff during all the studies. In the ITT population, all of the completed participants received $>75\%$ of their planned injections through 3 years of treatment.

EFFICACY

The mean CSMS after the 2013 grass pollen season after subcutaneous immunotherapy (SCIT) was significantly decreased in the active group, from 2.15 (range, 1.27–3.00) to 1.13 (range, 0.79–1.36) ($p = 0.03$) compared

with the placebo group, which decreased from 2.31 (range, 1.42–2.97) to 2.08 (range, 1.22–2.86) ($p = 0.28$). During the 3-year follow-up, the CSMS remained at a similarly low level, after termination of treatment in the study group, and it was significant compared with the placebo group. The detailed data of the CSMS, dSS, and dMS before SCIT, after 3 years of treatment, and the next 3 years of observation are shown in Table 2.

Free days of symptoms increased from an average 6 standard deviation of 10.1 ± 5.2 days at baseline up to 18.7 ± 6.3 days after AIT in the active group ($p = 0.02$) and remained at the same level, 16.1 ± 5.9 days ($p = 0.04$), which was significantly greater in comparison with baseline. In the placebo group, free days of symptoms were as follows: 8.7 ± 7.2 days at baseline, 9.4 ± 6.3 days after 3 years of placebo, and 9.1 ± 5.2 days at the end of observation (nonsignificant changes, $p > 0.05$).

IMMUNOLOGIC PARAMETERS

Allergen sIgE and sIgG4 measurements are presented in Figs. 3 and 4. The decrease of the mean serum concentration of sIgE Phl p5 in the study group was observed during AIT and further follow-up. However, the significant difference in comparison with placebo was noticed only after the final point of observation. The significant increase of sIgG4 Phl p5 in the blood serum in the active group was observed after AIT and until observation was over. The IgE/IgG4 ratio for Phl p5 decreased significantly, from 0.945 ± 0.883 to 0.298 ± 0.244 after three seasons of SCIT in the active group and did not significantly increase, up to 0.378 ± 0.144 ($p < 0.05$). There were no significant changes in the placebo group (0.811 ± 0.596 versus 0.892 ± 0.677 versus 0.763 ± 0.229 ; $p > 0.05$). Changes of the nasal response to grass allergen during the study between the active group and placebo are presented in Fig. 5.

QUALITY OF LIFE

The RQLQ results showed a mean baseline level of 1.51 (95% confidence interval [CI], 1.21–1.84) in the randomized patients. The mean final result was significantly decreased, to 1.01 (95% CI, 0.93–1.87) in the active group after 3 years of AIT ($p = 0.03$). During further observation, the RQLQ remained stable, between 0.97 and 1.26 (95% CI, 0.88–1.82) and was still significantly ($p > 0.05$) better than in the placebo group (1.52 [95% CI, 1.61–1.74] during the whole observation period).

DISCUSSION

The long-term clinical and immunologic effects after the end of AIT are still being studied with great interest.^{11–14} The unique feature of this study was its prolonged observation of elderly patients after receiving

Table 2 Efficacy of AIT during therapy and follow-up in comparison with placebo*

	Baseline	After AIT or Placebo	Follow-up		
			1 y	2 y	3 y
AIT ITT (<i>n</i> = 33)					
CSMS	2.15 ± 1.04#	1.13 ± 0.73§	1.39 ± 0.56¶	1.32 ± 0.69*	1.41 ± 0.72§
dSS	1.12 ± 0.65#	0.53 ± 0.21	0.56 ± 0.24**	0.61 ± 0.31##	0.47 ± 0.50§
dMS	1.08 ± 0.46#	0.41 ± 0.29§	0.38 ± 0.24¶	0.47 ± 0.31§	0.52 ± 0.29§§
Placebo ITT (<i>n</i> = 29)					
CSMS	2.31 ± 1.13#	2.08 ± 0.65§	2.19 ± 1.01¶	2.43 ± 1.15§	2.41 ± 1.11§
dSS	1.22 ± 0.44#	1.17 ± 0.29	1.26 ± 0.49**	1.17 ± 0.19##	1.15 ± 0.84§
dMS	1.17 ± 0.51#	1.43 ± 1.01§	1.35 ± 0.39¶	1.38 ± 0.42§	1.02 ± 0.4§§
AIT mITT (<i>n</i> = 27)					
CSMS		1.29 ± 0.88§	1.42 ± 0.69§	1.39 ± 0.72§	1.48 ± 0.58##
dSS		0.43 ± 0.21##	0.79 ± 0.31**	0.72 ± 0.27##	0.69 ± 0.32**
dMS		0.41 ± 0.29¶	0.62 ± 0.19¶¶	0.69 ± 0.35**	0.74 ± 0.31
Placebo mITT (<i>n</i> = 22)					
CSMS		2.19 ± 0.59§	2.34 ± 0.95§	2.55 ± 1.28§	2.09 ± 1.51##
dSS		1.13 ± 0.42##	1.07 ± 0.36**	0.98 ± 0.78##	1.34 ± 0.52**
dMS		0.93 ± 0.48¶	1.11 ± 0.27¶¶	1.58 ± 0.51**	1.29 ± 0.37

AIT = Allergen immunotherapy; ITT = intention-to-treat population; CSMS = combined symptoms medication score; dSS = symptoms score; dMS = medication score; mITT = modified intention-to-treat population.

*The mean weekly score in the grass pollen season; all data are mean ± standard deviation.

#p = not significant.

§p = 0.01.

¶p = 0.02.

||p = 0.04.

**p = 0.03.

##p = 0.05.

§§p = 0.06.

¶¶p = 0.07.

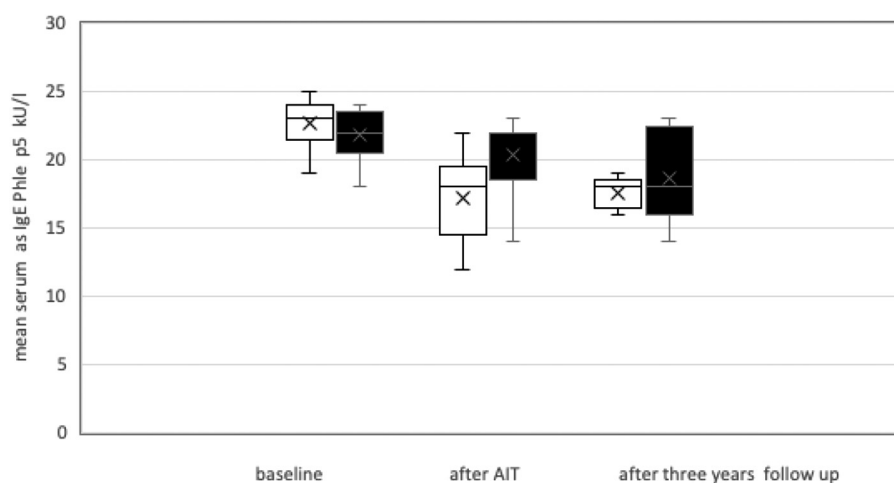


Figure 3. The mean serum concentration of immunoglobulin E (IgE) to Phl p5. The white box indicates the study group, the black box indicates the placebo group.* p = 0.034 (Chi-Squared test).

injected AIT for grass pollen allergy. This prolonged effect can be compared with other observations in younger groups.^{11,12} There was evidence that a

prolonged effect of AIT in the elderly patient was observed after sublingual immunotherapy to house-dust mites or grass pollen.^{15,16}

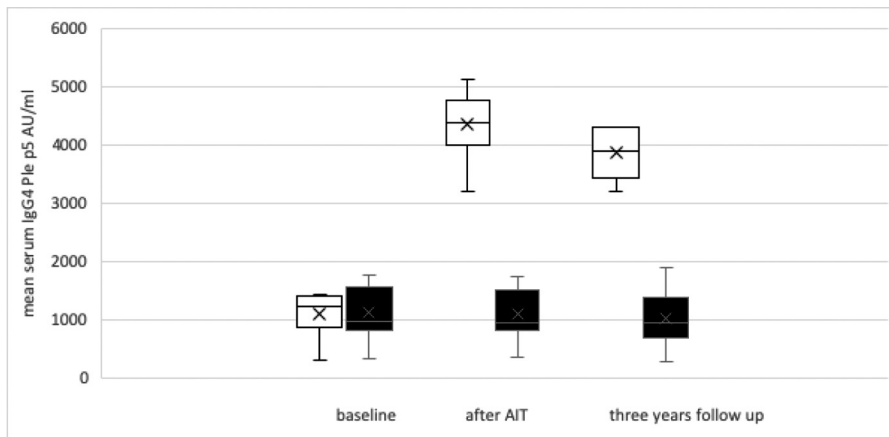


Fig. 4 The mean serum concentration of immunoglobulin G4 (IgG4) to Phl p5. The white box indicates the study group, the black box indicates the placebo group.* $p=0.02$, ** $p=0.01$ (Chi-Squared test).

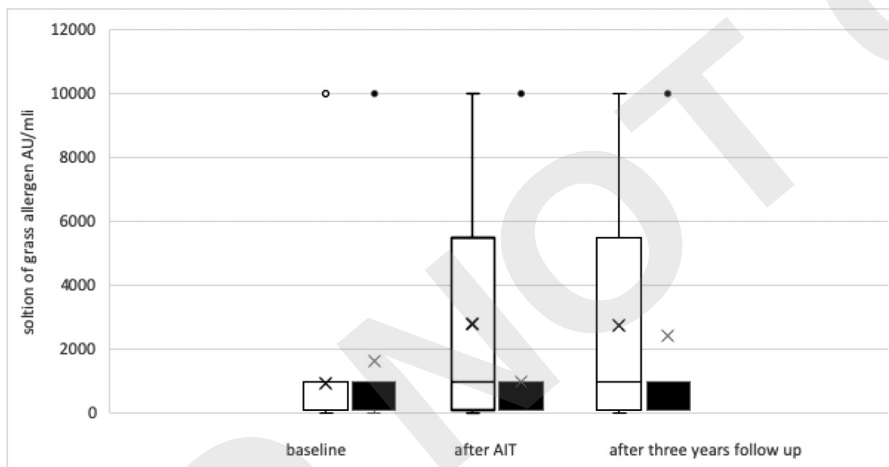


Figure 5. Changes of the nasal response to grass allergen during the study between the active group (white boxes) and placebo (black boxes). *Significant changes between the active and placebo groups in nasal response to grass allergen (Chi-Squared test).

In this study, the significant decrease in the CSMS, despite preseasonal treatment, persisted at a similar satisfactory level 3 years after AIT. This was especially visible compared with the placebo. Additional evidence of this was a good quality of life in the active population, which was still maintained 3 years after the end of AIT. In addition, it was valuable because there were elderly patients. Good adherence in the study group was noteworthy and contributed to obtaining valuable final results. This might be an important argument for using AIT in the elderly as well as the fact that the immunologic parameters were also promising, even after 3 years of follow-up, especially the increase of the IgG4 level. The same immunomodulatory effect has been observed in young patients, despite the aging of the immune system.

However, the response of nasal mucosa to different solutions of grass allergen was not so obvious in all

patients undergoing desensitization. In some, despite the good clinical effect after desensitization, the nasal mucosa reacted in the same way to the administered allergen as before desensitization. Perhaps this is because the sensitivity of the nose is lower in older patients. Nasal provocation has limitations in assessing the effectiveness AIT. The lack of allergen provocation chambers, which are currently recommended, was a limitation of the study.¹ The Purethol used in the study is an allergoid of high efficacy and safety regardless of the dosage regimen and type of allergen; this finding was confirmed in studies.^{17,18} In addition, reducing the need for symptomatic drugs and primary reliance on antihistamines improved the safety profile of treatment for the elderly. It should be remembered that this reduces the chances of polytherapy.

There were some limitations to the study. Despite the fact that the expected group number was obtained

before the study analysis, the number of patients was relatively small. These groups were comparable with those in other similar studies, in which there was a problem with the proper selection of patients >65 years of age for AIT.^{15,19,20} The use of preseasonal AIT is certainly less effective; however, due to the age of the patients, the desensitization protocol was more user-friendly for this age group.

However, the current position paper allows the use of this method of treatment.² We also did not assess the impact of individual pollen seasons on the obtained results. It seems that this could affect the trends observed in both the study and placebo groups. It is important to remember that the grass mix, but not Phl p5 itself, was used in the diagnostic procedures, and Purethal contained a grass mix (but not only Phl p5). The high allergen cross-reactivity between grasses and the high concentration of Phl p5 in Purethal (26.3 µg/mL) could explain these differences; however, it cannot be ruled out that this could affect the final results.

CONCLUSION

The positive effect obtained for 3 years after pre-seasonal AIT for grass pollen allergy was sustained after 3 years of AIT, which provided a substantial advantage to elderly patients. There is a need for similar prospective and observational studies in larger groups of patients.

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