

Grass pollen sublingual immunotherapy: A double-blind, placebo-controlled study in elderly patients with seasonal allergic rhinitis

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ABSTRACT

Background: This study evaluates the safety and efficacy of specific sublingual immunotherapy (SLIT) against grass pollen allergens in patients >60 years of age with seasonal allergic rhinitis (SAR) and/or asthma. This study sought to assess nasal symptoms during the grass pollen season, reduce medication use, and monitor adverse reactions during immunotherapy.

Methods: Seventy-eight 60- to 70-year-old patients with SAR and a confirmed grass pollen allergy according to skin-prick tests, nasal provocation, and measurement of serum IgE were included in the study. The patients were individually randomized to the active or placebo groups using a double-blind method. A total of 41 subjects in the SLIT group (5 grass pollen mixture) and 37 subjects in the placebo group were monitored for 3 years. The patients were required to record each use of an antiallergy medication on a diary card.

Results: Thirty-eight patients completed 3 years (preseasonal) of SLIT, and 34 subjects finished the placebo treatment in the same time period. The total nasal symptom score decreased by 64% in the active group and 7% in the placebo group after SLIT. This difference was only significant in the active group ($p < 0.05$). At the end of therapy, the total medication score of the active group decreased significantly by a maximum of 51% ($p < 0.05$), whereas the total medication score of the placebo group had an insignificant decrease. None of the study participants had systemic adverse reactions during the study period.

Conclusions: SLIT in elderly patients with a grass pollen allergy generated a significant clinical improvement in the active group compared with the placebo group for grass pollen season. This therapy was well tolerated.

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Atopic diseases, such as seasonal and perennial allergic rhinitis, bronchial asthma, and allergic dermatoses, are often under diagnosed and untreated in elderly patients. The guidelines for the diagnosis and treatment of allergic diseases rarely focus on the elderly population. However, allergic rhinitis and asthma caused by inhaled allergens, such as pollens, are more common in patients >60 years of age.^{1,2} Therefore, it is critical that the new allergy treatment methods that are commonly used in young people be investigated for their efficacy in elderly people. Allergen-specific sublingual immunotherapy (SLIT) is a safe and effective treatment method, especially for allergic rhinitis. Several studies have confirmed this therapy's efficacy in young people.^{3–5} Grass pollen is a major allergen for patients with allergies, and there have been several randomized controlled immunotherapy trials with a high degree of safety and efficacy.^{6–10} Despite the lack of objective contraindications, specific immunotherapy has not had a significant role in treating elderly patients, which may be caused by the lack of safety evidence in this group. Finally, there is also a question of whether immunotherapy can produce sufficient allergen tolerance in patients with an aging immune system.

The aim of this study was to assess the safety and efficacy of SLIT for grass pollen allergens in elderly patients with seasonal allergic rhinitis and a confirmed grass pollen allergy.

METHODS

Patients

Seventy-eight patients, 60–70 years of age, were recruited from the Outpatient Allergy Clinic to assess their eligibility for inclusion in the study. The subjects with moderate or severe intermittent allergic rhinitis who fulfilled the Allergic Rhinitis and Its Impact on Asthma (ARIA) guidelines criterion¹¹ had a positive skin-prick test, were positive for specific IgE (sIgE), and had positive nasal provocation tests (NPTs) with grass pollen mixture allergens were included in the study. Patients with any of the following characteristics were excluded: hypersensitivity to other allergens, nonallergic rhinitis (especially senile or vasomotor rhinitis), and severe nonstable diseases (especially bronchial asthma). However, stable coronary disease; diabetes; arterial hypertension; and well-controlled, mild, or accidental atopic bronchial asthma were permitted. All subjects were required to abstain from antiallergy drugs and glucocorticoid nasal drops for at least 6 weeks before the start of the study.

The patients were individually randomized in equal numbers to one of two “parallel” groups, the active or placebo treatment group, using a double-blind method. A total of 41 subjects in the SLIT group and 37 subjects in the placebo group were monitored for 3 years. The groups were comparable at baseline (Table 1).

Diagnostic Procedures

A careful examination of the eyes, ears, nose, and throat was performed on all patients. The patients with other nasal problems, such as chronic nasal obstruction, reduced olfaction, bacterial colonization, and chronic sinusitis, were diagnosed based on a computed tomography scan and nasal endoscopy. As a result of these problems, some patients were excluded from further observation. The subjects with other chronic or acute clinical disorders or with a history of respiratory tract infections within 4 weeks before the investigation were also excluded. The skin-prick test was performed using inhalant allergens (Stallergenes, Antony, France) from the following panel: *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, mixed five grasses (*Phleum pratense*, *Dactylis glomerata*, *Anthoxanthum odoratum*,

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Table 1 Characteristics of patients before randomization

	Active	Placebo	<i>p</i> Value
Age (yr)	63.18 ± 3.12	64.13 ± 2.92	0.782
Male/female ratio	22/19	19/18	0.423
Duration of rhinitis (yr)	11.7 ± 7.5	10.9 ± 8.41	0.145
No. of subject with asthma	3	2	0.89
No. of patients with eczema	2	3	0.223
No. of smokers	4	3	0.631
No. of patients with stable coronary disease	6	7	0.657
No. of patients with arterial hypertension	14	11	0.341
No. of patients with diabetes	3	2	0.233
Mean weekly nasal symptom score	5.811 ± 1.954	5.370 ± 1.34	0.187
Mean weekly nonnasal symptom score	4.083 ± 0.854	4.191 ± 0.568	0.177
Mean weekly medication score	0.877 ± 0.129	0.912 ± 0.201	0.543
Total IgE	401.27 ± 87.15	431.91 ± 98.11	0.401
sIgE to grass pollen	36.29 ± 11.42	40.11 ± 9.03	0.156
Mean symptom score after NPT to grass pollen	6.11 ± 3.7	5.071 ± 2.04	0.225
Mean percent of nasal flow decrease after NPT to grass pollen	91.5	90.8	0.198
Moderate seasonal allergic rhinitis (according Global Initiative for Asthma)	18	16	0.022
Severe seasonal allergic rhinitis (according Global Initiative for Asthma)	23	21	0.116

sIgE = serum concentration of specific IgE; NPT = nasal provocation test.

Lolium perenne, and *Poa pratensis*), mixed tree, mugwort, *Alternaria*, *Cladosporium*, dog, and cat allergens. Positive (10 mg/mL of histamine) and negative (saline) controls were included. A grass pollen allergy was defined as having positive skin tests for five grass pollen allergens with a minimum wheal diameter of at least 3 mm greater than that elicited by the negative control.¹² Those patients with negative tests for histamine sensitivity were excluded from further analysis. The sIgE reactivity to the single grass pollen allergen components (Phl p1, Phl p2, Phl p5, Phl p6, Phl p7, and Phl p12) was determined using ImmunoCAP (Phadia AB, Uppsala, Sweden) tests. The results were considered positive when the sIgE concentration was >0.35 IU/mL (according to the manufacturer's instructions). NPTs using active anterior rhinomanometry with commercial grass pollen mixture allergens (Allergopharma, Reinbeck, Germany) were performed using the methods described by Bachert *et al.* and Dordal *et al.*^{13,14} A reduction in the peak nasal inspiratory flow ≥40% and an increase in symptoms ≥5 points were considered by Bachert *et al.* and Dordal *et al.*^{13,14} to be positive NPT criteria. The NPTs were also repeated after 3 years of treatment. Patients sensitized only to grass pollen were included in this study.

Treatments

The patients were randomly selected to receive oral Staloral 300 SR 5 grass pollen mixture extract solution of *P. pratense*, *D. glomerata*, *A. odoratum*, *L. perenne*, and *P. pratensis* (Stallergenes) or placebo (Fig. 1). The recruitment period was limited to 3 months (October–December). SLIT was performed by the build-up schedule in 4 days (30–60–120–240 IR), as suggested by the manufacturer, starting in the month of January. A maintenance dose of 240 IR was then administered five times a week until the end of April. Each dose had to be taken in the morning before breakfast, and the allergen drops had to be kept under the tongue for at least 2 minutes before swallowing. Using this schedule, an average cumulative dose of 225 µg of Phl p5 was administered to each patient undergoing active treatment for all 3 years of the study. The Staloral and placebo were dispensed in drops from bottles with identical appearance. These treatments were prepackaged in bottles and consecutively numbered for each participant according to the randomization schedule. Each patient was assigned an order number and received the box corresponding to the prepackaged bottles. The volume of residual SLIT medication was assessed for every patient. When necessary, the patients were allowed to take

the following drugs: antihistamine (5 mg of desloratadine tablets), intranasal corticosteroid (mometasone), topical ocular antihistamine drops (ebastine), and a 4-mg tablet of methylprednisolone. Other antiallergic drugs were not permitted during the study. The nasal corticosteroid was the first-line treatment. The patients recorded the use of medications on their diary cards, and a specific weekly score was assigned (1 point, used only nasal corticosteroids or eye drops at a minimum of 1 day/wk; 2 points, the previous therapy plus 1 tablet of levocetirizine at a minimum of one per day; 3 points, the previous therapies plus one 4-mg tablet of methylprednisolone at a minimum of one per day). The number of participants who completed the study is shown in Fig. 1.

Symptoms and Diary

The patients' allergic rhinitis symptoms were monitored using a 7-point visual graphic scale (published by the Joint Task Force and modified by ARIA) for grading the severity of nasal (sneezing, runny nose, congestion, itchy nose, and postnasal drip) and nonnasal (eye symptoms, throat symptoms, chronic cough, ear symptoms, and headache) symptoms in addition to mental function and quality-of-life changes.¹⁵ This scale was based on the patients' diaries, which were completed during the 3-year observation grass pollen period in Poland (May–July), when SLIT was instituted and 1 year before starting. The patients' peak expiratory flow was measured each day before administering SLIT, and the patients were monitored for possible adverse reactions for 30 minutes after SLIT administration.

The statistical analysis was performed using Statistica Version 8.12 (SoftPol; Cracow, Poland). The Student's *t*-test for unpaired data was used to analyze differences in the medication and symptom scores, NPT scores, sIgE, and IgE. The Wilcoxon test was used to analyze other differences between the groups. The chi-square test was used to analyze differences between the NPT flow and the rate of adverse events in each study group. A correction for multiple comparisons for the heating season was performed. The differences were considered significant at *p* < 0.05. The study was approved by the local ethics committees of Medical University of Silesia in Poland. All patients signed an informed consent form.

RESULTS

Thirty-eight patients completed 3 years of SLIT, and 34 subjects finished the placebo treatment within that time frame. Four patients

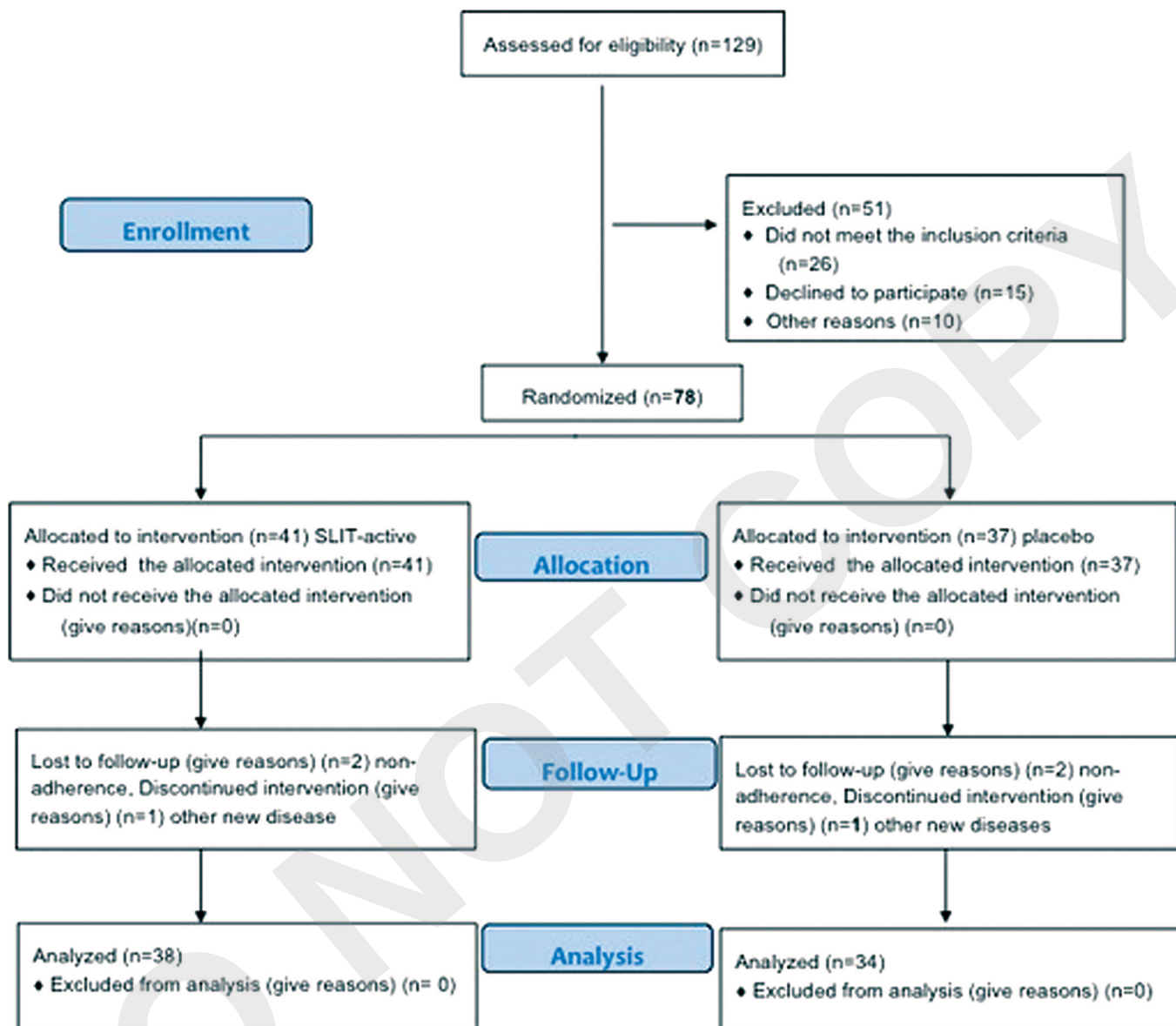


Figure 1. Number of participants assessed for eligibility who completed the study.

in the active group and nine patients in the placebo group prematurely terminated study participation, as shown in Fig. 1. The nasal symptom scores of the active group and the placebo group were significantly different at the end of the study (Table 2); however, there was no such difference in the nonnasal symptoms. The total nasal symptom score decreased by 64% (5.811 ± 1.954 versus 2.106 ± 0.822) in the active group and 7% (5.370 ± 1.34 versus 5.023 ± 0.991) in the placebo group after 3 years of treatment. This difference was significant only in the active group ($p < 0.05$). Detailed data of the subsequent years are summarized in Table 3.

AFTER 3 YEARS OF SLIT

Medication Scores

After 3 years of preseasonal treatment, the total medication score started to significantly decrease in the active group. The total medication score decreased by a significant 51% in the active treatment group ($p < 0.05$) but did not decrease significantly in the placebo group ($p = 0.38$). Additionally, the medication scores were signifi-

cantly lower in the active group than in the placebo group at the end of the study (Table 2).

Safety Assessment

Neither group experienced systemic adverse reactions or severe local reactions during the course of the study. Five patients in the active group had local immediate, adverse reactions (oral pruritus, four patients; facial flushing, one patient) that spontaneously resolved. There was no need to reduce the SLIT dosage. There were no delayed reactions. In the placebo group, there were no adverse reactions.

Nasal Provocation Test and Immunologic Parameters

The active group exhibited decreased reactivity of the nasal mucosa after grass provocation over the 3-year course of SLIT treatment compared with the placebo group ($p < 0.05$); however, the clinical symptom score reactions during the provocations were unchanged

Table 2 Clinical and laboratory parameters of all subjects after 3- year treatment phases

	Active	Placebo	<i>p</i> Value
Mean weekly nasal symptom score	2.106 ± 0.822	5.023 ± 0.991	0.008
Mean weekly nonnasal symptom score	2.908 ± 0.696	3.898 ± 0.244	0.034
Peak flow measurement value before medication use (L/min)	340.1 ± 11.21	372 ± 13.3	0.197
Mean weekly medication score	0.429 ± 0.115	0.885 ± 0.201	0.009
Total IgE at 36 mo (kU/L)	387.5 ± 87.11	396.7 ± 90.04	0.071
Specific IgE to grass at 36 mo (kU/L)	32.77 ± 10.83	36.8 ± 11.30	0.065
Mean symptom score after NPT to grass pollen	5.523 ± 2.1	5.451 ± 1.544	0.403
Mean percent of nasal flow decrease after NPT to grass pollen	67.5	88.7	0.02
Mild seasonal allergic rhinitis after SLIT	23	3	0.001
Moderate seasonal allergic rhinitis after SLIT	13	18	0.054
Severe seasonal allergic rhinitis after SLIT	5	16	0.001

IgE refers to the serum concentration of IgE.

NPT = nasal provocation test; SLIT = sublingual immunotherapy.

Table 3 Score of the nasal symptoms in the following grass pollen seasons 1 year before and during SLIT therapy

<i>n</i> = Total Daily Measurements	Score of the Nasal Symptoms as the Mean From All Months of the Grass Pollen Season			
	V–VII 2010*	V–VII 2011	V–VII 2012	V–VII 2013
Active	5.811 ± 1.954	3.401 ± 0.788	2.301 ± 0.541	2.106 ± 0.822
Placebo	5.370 ± 1.34	4.981 ± 0.412	5.134 ± 0.856	5.023 ± 0.991
<i>p</i>	NS	0.012	0.009	0.008

*Grass pollen season before the start of treatment.

NS = not statistically significant; SLIT = sublingual immunotherapy.

(Table 2). The other analyzed parameters, such as the as total and sIgE, were not significantly changed in either group (Table 2).

DISCUSSION

To the best of our knowledge, this is one of two double-blind, placebo-controlled SLIT trials performed in elderly patients.¹⁶ Immunotherapy in patients >60 years of age is uncommon. However, the prevalence of IgE-dependent allergic rhinitis and other atopic diseases in elderly patients is reportedly increasing. This increase is relevant because of the aging world population and the global trend of increased allergic diseases.^{1,2,11,17} An important issue in this study was the difficulty in identifying the elderly patients with only allergic rhinitis and no other ear, nose, and throat problems, which significantly reduced the target group of respondents.

According to the criteria defined by Malling, the efficacy of immunotherapy in double-blind, placebo-controlled trials must be supported by symptom and medication score improvements of >30%.¹⁸ In this study, the active treatment group showed 64% (nasal symptom reduction) and 51% (medication score reduction) improvement in grass pollen season (May–July in Poland). These results also indicate that the aging immune system does not have a significant influence on the effectiveness of immunotherapy. However, typical aging of the oral mucosa was most likely responsible for only a small number of the side effects, which was also observed in another study.¹⁶ The similar issue of the aging nasal mucosa in elderly patients most likely caused fewer allergic rhinitis symptoms in this group than in young patients. Aging most likely resulted in relatively low nasal symptom scores. For this reason, we used the seven-point visual analog scale, which easily detects small differences in nasal reactions. Diaries were filled on a weekly basis to simplify this procedure for elderly patients. Naturally, this approach could slightly reduce the reliability of the observations.

The efficacy of 3 years, preseasonal SLIT therapy for grass pollen allergies in the elderly is comparable with the data we previously reported for younger patient populations with allergic rhinitis.^{8,10,19–23}

This suggests that we observed the same immunomodulation effect as seen in young patients despite the aging of the immune system.²⁴ In addition, reducing the need for symptom-targeted drugs, primarily antihistamines, improves the safety profile of treatment for elderly patients. In older patients, the most frequent adverse reactions are to antihistamine drugs.^{11,16} This observation is not isolated. However, this finding provides evidence that immunotherapy in elderly patients, despite its low popularity, should be more frequently considered for treating allergic rhinitis. Unfortunately, all except one of the few studies that support the safety and effectiveness of immunotherapy in the elderly are not blinded.^{16,21,25} Of course, this gap in the literature requires further controlled studies in this area. Furthermore, one major problem is determining whether elderly patients qualify for immunotherapy. In addition to clear indications, such as allergies, other overlapping diseases must be excluded. In the case of the patients analyzed in this study, those who were excluded were mainly those with senile rhinitis and vasomotor rhinitis. Despite a clear diagnosis of a grass pollen allergy and positive NPTs, other diagnoses can not be ruled out in some patients. The challenge is that ARIA emphasizes a specific mechanism associated with rhinitis in elderly patients.¹¹ Another challenge is the coexistence of other serious chronic diseases, which are often unstable and preclude immunotherapy. Patients with such diseases were excluded from this study. However, mild stable cardiovascular disease and type 2 diabetes did not affect the safety of immunotherapy in the patient population we studied and *vice versa*. This study supports the use of immunotherapy in elderly patients through the demonstration of a good safety profile without any systemic reactions during 3 years of therapy. This study is in agreement with observations that have previously been made.^{16,26} The results of the NPT emphasize its value only in diagnosing allergies but not in monitoring the effectiveness of immunotherapy, which is not in agreement with previously published data.^{16,27} A lack of change in the concentration of allergen-specific IgE or total IgE in the serum supports the idea that this

marker is not valuable for monitoring the efficacy of immunotherapy; however, this topic is still under discussion in the literature.^{28,29}

In conclusion, this study showed that SLIT to grass pollen allergens resulted in a significant clinical improvement in the active group compared with placebo group during pollen seasons. This therapy was well tolerated. These observations may lead to the more frequent use of SLIT immunotherapy in elderly patients. However, further controlled studies are required to assess this oral treatment, especially with other allergens, and injection-based treatment studies should also be performed.

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