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Subcutaneous allergen-specific immunotherapy with *Gramineae* pollen in children with allergic rhinoconjunctivitis

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Abstract

Aim: Patients experiencing persistent complaints of moderate-severe allergic rhinoconjunctivitis despite symptomatic treatment are considered candidates for Allergen Specific Immunotherapy (ASIT). The present study aims to assess the effectiveness and safety of ASIT using *Gramineae* pollen in children afflicted by allergic rhinoconjunctivitis.

Materials and Methods: The study involved participants between 5 and 18 years of age who had allergic rhinoconjunctivitis. These participants were divided into two distinct groups. The initial group underwent ASIT, while the other constituted the control group that refrained from it. The control group comprised participants with akin ages and equivalent disease durations. Visual analog scores (VAS), daily symptom scores (dSS), daily medication scores (dMS), and combined symptom and medication scores (CSMS) were assessed at three specific time junctures: Baseline, post the initial year of ASIT, and after the second year of ASIT.

Results: The study encompassed 188 children who had been diagnosed with allergic rhinoconjunctivitis. Among these, 94 patients had undergone immunotherapy. Of the total cases, 105 (55.9%) were male, with a median age of 14 years (range: 7-18 years). Among the patients who had received ASIT, there were statistically significant reductions in VAS, dSS, dMS, and CSMS after one and two years of therapy when compared to the baseline values ($p<0.001$). Upon comparing the group receiving ASIT with the control group after a two-year follow-up, notable reductions were observed in VAS, dSS, dMS, and CSMS ($p<0.001$). Five patients (5.3%) experienced systemic reactions.

Conclusion: The current study demonstrated that ASIT with *Gramineae* pollen is clinically effective in patients with *Graminae* pollen-induced allergic rhinoconjunctivitis.

Introduction

Allergic rhinoconjunctivitis (ARC) stands as the most widespread allergic condition, inducing numerous comorbidities and negatively impacting the quality of life [1,2]. Despite allergen prevention and pharmacological treatment being the primary approach for allergic rhinitis (AR), these methods might not deliver sufficient clinical enhancement for every patient [3]. Allergen-specific immunotherapy (ASIT) is specifically indicated for patients experiencing moderate-severe ARC, whose symptoms persist despite symptomatic interventions [4]. Allergen-specific immunotherapy (ASIT) represents the singular natural-altering treatment for allergic disease. It forestalls new sensitizations, diminishes symptoms, and curtails the risk of asthma development [5-7]. Numerous distinct studies analyzing clinical outcomes of ASIT trials have been documented to ascertain ASIT's effectiveness [8]. These disparities in methodologies across studies have posed substantial challenges in appraising the efficacy of allergen immunotherapy. To gauge the effectiveness of allergen-specific immunotherapy, the amalgamation of symptom and medication scores is employed. Consequently, the EAACI Immunotherapy Interest Group's Task Force recommends a consistent and standardized method: the amalgamated symptom and medication score [9].

In Turkey, exploration into the effectiveness and safety of treatments for children with ARC remains limited. This study sought to evaluate the effectiveness and safety of allergen-specific immunotherapy (ASIT) involving *Gramineae* pollen [Allergovit® grasses (60%) + secale cereale (40%), Allergopharma GmbH & Co. KG] in chil-

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dren diagnosed with moderate-severe seasonal ARC over a two-year treatment span.

Materials and Methods

Subjects

The children diagnosed with moderate-severe seasonal ARC and who had received treatment with medication and/or ASIT and followed up in the Pediatric Allergy and Immunology Department of at the three Faculty of Medicine Hospitals (Inonu University, Medeniyet University, and Gazi University) from March 2016 to September 2018 were contained in the current study. In season, cases were also taken standard medication according to the principle of the ARIA [10]. As a control group, the matched group in which participants diagnosed with ARC have similar ages and similar duration of disease were included. Demographic information about the patients and reactions developed during follow-up were recorded from the patient files.

The study inclusion criteria were (1) the cases who were 5-18 years of age, diagnosed with moderate-severe sessional AR with/without conjunctivitis, (2) "had *Gramineae* pollens" sensitization that was identified by skin test or specific Ig E measurements, (3) had received subcutaneous immunotherapy for at least 24 months.

The study exclusion criteria were (1) the patient who had co-existence of perennial ARC, (2) had file records missing, (3) had no asthma (4) had not completed two years of follow-up.

The research protocol was approved by the local ethics committee of Inonu University Faculty of Medicine with decision number 2019/7-24, and all participants received their written informed consent.

Allergen-specific immunotherapy

The product under investigation (Allergovit®, Allergopharma GmbH & Co. KG) is an allergoid preparation of grasses (60%) + secale cereale (40%) pollen, adsorbed onto aluminum hydroxide and administered through subcutaneous injections. It was available in two concentrations: Strength A (1000 standardized therapeutic units [TU]/mL) and Strength B (10000 TU/mL). Strength B contained grasses (60%) + secale cereale (40%) pollen in a 0.6 mL maintenance dose. The treatment regimen comprised injections at weekly intervals, following the standard dosing plan: initial injections of 0.1, 0.2, 0.4, and 0.8 mL of Strength A, followed by 0.15, 0.3, and 0.6 mL of Strength B. The duration between injections was gradually extended to 2 weeks, then 3 weeks, and finally 4 weeks.

Allergen detection

Skin prick tests or specific IgE measurements in blood were performed to determine the sensitivity of the aeroallergen. The inhaled allergens (*Gramineae* pollens, house dust mites, cats, weeds, and molds) were used for allergen detection. These allergens are the most common sensitized allergens in our country [11]. Skin prick tests or specific Ig E measurements in blood were performed to identified the patient's sensitivity to inhaled allergens. Skin prick test was carried out according to standard protocol [12]. In the blood measurement, the specific Ig E level was $\geq$0.35 kU / L was considered positive.

Assessment of efficacy

The assessment of allergen-specific immunotherapy's effectiveness involved employing total daily symptom scores (dSS), daily medication scores (dMS), combined symptom and medication scores (CSMS), and visual analog scores (VAS). According to the EAACI Position Paper [9] recommendations, the total daily symptom score, dMS, and CSMS were evaluated. Baseline values for nasal symptoms, conjunctival symptoms, medication usage, and overall symptom severity were documented in patient files before ASIT. Following ASIT, patients reported their nasal symptoms, conjunctival symptoms, medication use, and overall symptom severity during pollen seasons. The evaluation of symptoms took place in the first and second years of treatment. Physicians assessed the total daily symptom score, dMS, CSMS, and VAS during seasonal visits. The total daily symptom score comprised the sum of four nasal and two conjunctival symptom scores, evaluated based on a 0-3 point scoring system [9] (Table 1). Daily medication scores were assigned on a 0-3 point scale, depending on medication use. Furthermore, CSMS was calculated as the sum of dSS and dMS, utilizing a 0-6 point scoring system [9] (Table 1). The visual analog score depicted overall symptom severity on a 10-cm visual analog scale [13]. A 10-point scoring system was employed to assess subjective symptoms, with "0" indicating no symptoms and "10" representing extremely severe symptoms.

Statistical analysis

The statistical analysis was conducted utilizing Statistical Package for Social Sciences (SPSS) 22.0 software (SPSS Inc., Chicago, IL, United States). Frequency and percentage were used to express qualitative variables, while quantitative variables were presented as medians. The Kolmogorov-Smirnov test was employed to assess the normality of distributions. Nominal data underwent evaluation through Pearson's Chi-square or Fisher's exact test, as appropriate, while measurable data were subjected to comparison via the Mann-Whitney U test. Paired data were scrutinized using the Wilcoxon signed rank test for paired samples. The statistical significance threshold was established at $p<0.05$.

Results

Demographics

One hundred eighty-eight children with a diagnosis of ARC were included in the study. Ninety-four of the cases had received immunotherapy. One hundred and five of the cases (55.9%) were male, 83 cases (44.1%) were female, the median age was 14 (min-max: 7-18 years) and the median duration of complaints was 5 (min-max: 2-15 years). Twenty-two of the patients (11.7%) had a history of atopic eczema and 5 (2.7%) had food allergies. Sixty of the patients (32.1%) had passive cigarette exposure and 16 (8.5%) lived in the rural area. There was no difference among the immunotherapy group and the control group in terms of demographic data such as age, gender, duration of complaints, comorbidities atopic disease (Table 2).

Table 1. Nazal ve medication score [9].

a) Symptom score		
		0 = no symptoms 1 = mild symptoms (sign/symptom present, but minimal awareness; easily tolerated) 2 = moderate symptoms (definite awareness of sign/symptom that is bothersome but tolerable) 3 = severe symptoms (sign/symptom that is hard to tolerate; causes interference with activities of daily living and/or sleeping)
Nasal symptoms (Score 0–3)	Nasal symptoms (Score 0–3)	
	Itchy nose 0–3	Itchy nose 0–3
	Sneezing 0–3	Sneezing 0–3
	Runny nose 0–3	Runny nose 0–3
	Blocked nose 0–3	Blocked nose 0–3
Conjunctival symptoms	Itchy/red eyes 0–3	Itchy/red eyes 0–3
	Watery eyes 0–3	Watery eyes 0–3
(Total) daily symptom score (dSS)*		0–3 (max score is 3, i.e. 18 points/divided by 6 symptoms)
b) Medication score		
	Oral and/or topical (eyes or nose) non-sedative H1 antihistamines (H1A)	1
	Intranasal corticosteroids (INS) with/without H1A	2
	Oral corticosteroids with/without INS, with/without H1A	3
(Total) daily medication score (dMS) 0–3 (max score is 3)	(Total) daily medication score (dMS) 0–3 (max score is 3)	
c) Combined symptom and medication score		
CSMS	dSS (0–3) + dMS (0–3)	0–6

*Max score 18/6 (i.e. 4 nasal symptoms, max score 12 and 2 conjunctival symptoms, max score 6) is optimal for studies of seasonal pollinosis. This could be modified for studies of perennial allergies (e.g. in mite-allergic patients), for example, max score 12/4 (i.e. 4 nasal symptoms with omission of eye symptoms). By assigning 0–3 for all individual symptoms and dividing by the total number of symptoms, the symptom range 0–3, and the maximum symptom score of 3 would remain the same.

Table 2. Demographic properties of patients.

Variable	Group 1 (ASIT received) n: 94	Group 2 Control n:94	p-value
Age, median (min-max), year	14 (7-18)	15 (10-17)	0.645
Male gender	57 (60.6)	48 (51.1)	0.186
Duration of complaints, median (min-max), year	6 (2-15)	5 (2-10)	0.074
Comorbidities atopic disease			
History of atopic eczema	10 (10.6)	12 (12.8)	0.821
Food allergy	5 (5.3)	-	NC
Parental allergic rhinitis	34 (36.2)	28 (29.8)	0.352
Breastfeeding > 6 months	88 (93.6)	82 (87.2)	0.137
Passive exposure to cigarette	28 (30.1)	32 (34)	0.564
Pet in home	8 (8.5)	12 (12.8)	0.478
Living in a rural area	7 (7.4)	9 (9.6)	0.794
Monthly income >500 $	33 (35.1)	39 (41.5)	0.368

Group 1: Received allergen-specific immunotherapy, Group 2: Not received allergen-specific immunotherapy.

Efficacy of allergen-specific immunotherapy

In the group of patients who received immunotherapy; there were statistically remarkable decreases in dSS ($p<0.001$), dMS ($p<0.001$), CSMS ($p<0.001$), and VAS ($p<0.001$) through one and two years of therapy in com-

Table 3. Effectiveness of allergen-specific immunotherapy 2-year follow-up period (n: 94).

	Baseline	1st year	2nd year	p-value
dSS, median (min.-max.)	2.5 (0.75-3)	1.25 (0-2.5)	1(0-2.5)	<0.001
dMS, median (min.-max.)	2(1-2)	1 (0-2)	0 (0-2)	<0.001
CSMS, median (min.-max.)	4 (2.75-5)	2 (0-4.5)	1.375 (0-4.5)	<0.001
VAS, median (min.-max.)	8 (3-10)	4 (0-8)	3 (0-8)	<0.001

dSS: (Total) daily symptoms score, dMS: (Total) daily medication score, CSMS: Combined symptom and medication score, VAS: Visual analog score.

Table 4. Comparison of study parameters between groups 1 and 2.

Variable	Group 1 (ASIT received) n: 94	Group 2 (Control) n: 94	p-value
Daily symptom score			
Baseline, n (%)	2.5 (0.75-3)	2 (1-3)	<0.001
End of study, n (%)	1 (0-2.5)	2 (1-3)	<0.001
p-value	<0.001	0.071	
Daily medication score			
Baseline, n (%)	2 (1-2)	2 (0-3)	0.475
End of study, n (%)	0 (0-2)	2 (0-3)	<0.001
p-value	<0.001	0.18	
Combined symptom and medication score			
Baseline, n (%)	4 (2.75-5)	4 (1-6)	0.003
End of study, n (%)	1.37 (0-4.5)	4 (1.3-6)	<0.001
p-value	<0.001		
Visual analog scales			
Baseline, n (%)	8 (3-10)	7 (3-9)	<0.001
End of study, n (%)	3 (0-8)	7 (3-9)	<0.001
p-value	<0.001	0.005	

Group 1: Received allergen-specific immunotherapy, Group 2: Not received allergen-specific immunotherapy.

parison to the baseline values (Table 3). Moreover, there was a remarkable difference in CSMS and VAS between 1-year and 2-year treatment ($p<0.001$, Figure A and B). In the control group, there was a remarkable increase in VAS compared to baseline ($p = 0.005$), but there was no statistically remarkable difference in dSS ($p = 0.071$), dMS ($p = 0.18$) and CSMS ($p = 0.251$) compared to baseline. When the group of patients receiving immunotherapy was compared with the control group after two years of follow-up, there was a remarkable decrease in dSS ($p<0.001$), dMS ($p<0.001$), CSMS ($p<0.001$) and VAS ($p<0.001$) (Table 4).

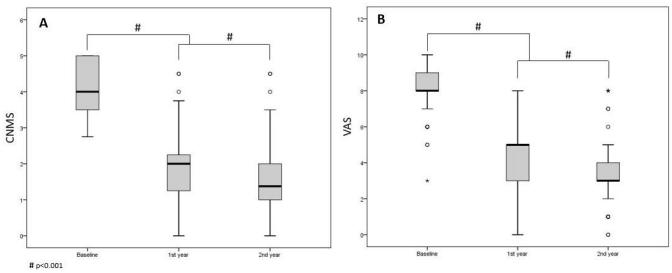

Figure 1. The significant differences in CSMS and VAS between 1-year and 2-year treatment in the patients who received allergen-specific immunotherapy.

Systemic side effects of allergen-specific immunotherapy

Systemic reactions occurred in five (5.3%) patients. Skin findings occurred in three patients, respiratory system findings occurred in two patients, cardiovascular system findings occurred in one patient, and anaphylaxis was developed in one patient. Throughout the entire therapy period, one patient discontinued the treatment because of anaphylaxis. These systemic reactions occurred in the initial phase of immunotherapy.

Discussion

The inclusion of allergen-specific immunotherapy emerges as a viable treatment approach for moderate-severe ARC cases wherein symptoms persist despite medical interventions. To gauge the effectiveness of ASIT, the employment of CSMS as a straightforward and standardized assessment method has been endorsed by the EAACI Immunotherapy Interest Group in recent times. The present study underscores the remarkable effectiveness of immunotherapy involving *Gramineae* pollens in addressing AR triggered by

such pollens. Substantiated by statistical analysis, our research demonstrates a noteworthy reduction in dSS, dMS, CSMS, and VAS scores among our AR patients who underwent ASIT during the follow-up period.

Considerable diversity is evident in the assortment of outcome parameters utilized across clinical trials involving ASIT [8]. Notably, the EAACI's immunotherapy Position Paper delineates nine key domains for clinical outcome measurement in ASIT for ARC: (1) Daily Symptom Score, (2) Daily Medication Score, (3) Combined Symptom and Medication Score, (4) Health-Related Quality of Life, (5) Visual Analog Score, (6) Well and Severe Days, (7) Global Assessments and Patient Satisfaction, (8) Rhinitis Control, and (9) Allergen Provocation Tests [9]. Presently, the Task Force of the EAACI Immunotherapy Interest Group advises the adoption of (a) a standardized nomenclature encompassing nasal and conjunctival symptoms categorized under six organ-related headings within the dSS, (b) a stepwise incorporation of rescue medication, culminating in the dSS, and (c) a scoring system for CSMS [9]. Our study employed dSS, dMS, CSMS, and VAS to assess the effectiveness of ASIT.

Allergen-specific immunotherapy fundamentally transforms the disease trajectory in patients grappling with respiratory allergies [10]. Extensive evidence underscores the effectiveness and favorable tolerability of allergen-specific immunotherapy for individuals, including both adults and children, contending with moderate-severe ARC [14-16]. A notable placebo-controlled study conducted by Worm et al. revealed that Birch pollen immunotherapy exerted a significant influence on CSMS. Over 3 years, the collective CSMS for treated patients exhibited a reduction despite the heightened birch pollen exposure [16]. In line with this, our study evidenced a significant decrease in CSMS during both the initial and subsequent years for patients who underwent immunotherapy involving *Gramineae* pollens over a two-year follow-up period.

Basic expectations from ASIT are clinical symptoms and decreased need for medication. In previous studies evaluating the effectiveness of ASIT, it was determined that there was a significant decrease in both symptom scores and medication scores in patients with allergic rhinitis [15,16]. When it comes to clinical effectiveness evaluations of ASIT, according to our research results, symptoms and medication scores were decreased. In parallel with previous studies, our study shows that the follow-up of patients treated with ASIT provides both a decrease in the symptoms and needs for medication.

The severity of systemic reactions to ASIT can differ from mild to severe adverse reactions [17]. The study that was performed by the Immunotherapy Interest Group of EAACI [18-19], it was demonstrated that ASIT for respiratory allergy was safe in general in the pediatric and adult population. In this study, systematic reactions were found in 2.1%. In our study, it was found 5.1% of all ASIT-treated patients. Only one reaction anaphylaxis occurred at the inanition phase of treatment.

There were a few limitations of our study. Firstly, we did not simultaneously count the pollen in the air to evaluate the effectiveness of immunotherapy. However, we think that our evaluation results were not affected because we evaluated the ASIT-received patients in the same period of the year and compared them with the control group. Secondly, we did not include a placebo group in our study. However, the fact that we used the control group suggests that our results were effective in their accuracy.

Conclusion

The current study demonstrated that ASIT with *Gramineae* pollens is clinically effective in patients with *Gramineae* pollen-induced ARC. This study has shown that systemic side effects developing during immunotherapy can be seen at a low rate.

Ethical approval

Ethical approval was received for this study from İnönü University Health Sciences Non-invasive Clinical Research Ethics Committee (decision no: 2019/7-24).

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