

Effects of Perennial Allergen Immunotherapy in Allergic Rhinitis in Patients with/without Asthma: A-Randomized Controlled Real-Life Study

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Keywords

Allergen immunotherapy · Allergic rhinitis · Asthma

Abstract

Background: There have been very few studies in real-life settings comparing the treatment effects of allergen immunotherapy (AIT) and pharmacotherapy for perennial allergic rhinitis (AR). **Objective:** This study was performed to compare AIT and pharmacotherapy in terms of their effects on the symptom control and quality of life (QOL) of AR patients with/without asthma. **Methods:** A total of 250 patients diagnosed with AR with/without asthma were included and assigned to the immunotherapy (AIT plus pharmacological treatment) or control (pharmacological treatment only) group. Clinical and medication scores, QOL scores, and lung function (forced expiratory volume in one second as a percentage; FEV1%) were measured at baseline and 3 years after the start of treatment. **Results:** This study showed that there was clinical improvement in AR symptoms in the AIT group, whereas standard pharmacotherapy alone had no significant effect on nasal symptoms. The QOL and satisfaction scores, as evaluated with a visual analogue scale (VAS), were further improved compared to the pharmacotherapy group. There was a significant improvement in medication scores in both AIT groups. According to our results, while total asthma scores and asthma control test scores were significantly im-

proved in the HDM AIT group, they did not change in the *Parietaria* pollen AIT group. In our study FEV1% was increased compared to the baseline value in the AIT group, but it was not statistically significant. On the other hand, FEV1% remained without any improvement in patients on standard pharmacotherapy. **Conclusion:** Perennial AIT was found to be superior to pharmacotherapy in decreasing symptoms as well as in improving QOL scores in AR patients with/without asthma. HDM AIT was more effective for asthma symptoms than *Parietaria* pollen AIT.

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Introduction

House dust mites (HDM) are the most important perennial allergen source worldwide and a significant cause of allergic rhinitis (AR) and allergic asthma [1]. *Parietaria* (*officinalis*, *judaica*, *lusitanica*, and *creatica*) is the most common pollen in the Mediterranean region. It has a very long period of pollination and first appears at the beginning of February and persists until December. Thus, it can be considered a perennial allergen [2]. To date, only one study has compared 2 perennial allergens; it showed that *Parietaria* pollen-associated AR is the same as the prev-

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alence of asthma and it is associated with more severe rhinitis than HDM-associated AR [3]. Until 2007, there was no specific test score for evaluating symptom control in AR. In 2007 Bousquet et al. [4] did an evaluation of symptom control in AR. They suggested that a visual analogue scale (VAS) score can be used for the Rhinoconjunctivitis Quality of Life (QOL) questionnaire [4]. In 2011 Demoly et al. [5] developed a self-assessment AR control test which had better patient outcomes. In patients with asthma and comorbid AR, Braido et al. [6] suggested a short daily asthma and rhinitis QOL assessment called RhinAsthma Patient Perspective (RAPP). RAPP is a simple 8-question questionnaire which provides a valid, reliable, and standardized health-related QOL measurement in practice. Allergen immunotherapy (AIT) is the only etiology-based treatment for allergic disease which has demonstrated a reduction in both new allergic sensitization and progression of the disease [7]. Although the evidence of its effectiveness in asthma is still a matter of debate, its efficacy in reducing the severity of symptoms related to AR has been identified in randomized controlled studies [8, 9]. The assessment of AIT efficacy is not well standardized and it is mainly based on symptom improvement and drug intake. Data from the literature suggests that the total symptom score (TSS), a VAS, and an asthma control test (ACT) could be useful parameters in clinical practice [10]. The duration of AIT is important in producing clinical tolerance. Numerous studies have shown that fewer than 3 years of treatment is not sufficient for AIT to produce clinical tolerance [11, 12]. Clinicians recommend that AIT should continue for at least 3 years for long-term clinical tolerance [13].

In this study we evaluated the effects of perennial AIT compared to pharmacotherapy. The primary outcome was a decrease in symptom scores at the end of 3 years of follow-up with either AIT or pharmacotherapy. The secondary aim was to compare the effectiveness of HDM AIT versus *Parietaria* pollen AIT.

Materials and Methods

Study Design

This study was planned as a randomized real-life controlled observational study.

Patients

HDM-monosensitized or *Parietaria* pollen-monosensitized adult patients (age 18 years or older) with perennial AR symptoms were included. To find patients monosensitized against either HDM or *Parietaria* pollen, a total of 12,790 AR patients with/without asthma were screened. Among them, 250 were monosensitized

(127 to HDM and 123 to *Parietaria* pollen). Patients who had uncontrolled or severe asthma, as well as polysensitized patients, were excluded from this study. Each patient was diagnosed based on Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines [14].

Asthma was diagnosed based largely on symptom patterns and the patient's history of having asthma, and patients were classified according to Global Initiative for Asthma (GINA) guidelines [5].

The patients then were randomized to treatment with only pharmacotherapy (control group) or AIT add-on pharmacotherapy (AIT group). The following groups were further formed within the AIT and control groups: group 1, HDM AIT without asthma; group 2, HDM AIT with asthma; group 3, *Parietaria* pollen AIT without asthma; group 4, *Parietaria* pollen AIT with asthma; group 5, HDM pharmacotherapy without asthma; group 6, HDM pharmacotherapy with asthma; group 7, *Parietaria* pollen pharmacotherapy without asthma; and group 8, *Parietaria* pollen pharmacotherapy with asthma.

Sensitization to Inhalant Allergens

The presence of specific immunoglobulin E (sIgE) was confirmed based on skin prick tests (SPT) and/or levels of serum sIgE to *Dermatophagoides farinea*, *D. pteronyssinus*, or *Parietaria* inhaled allergens. SPT were done for *D. farinea*, *D. pteronyssinus*, grass pollen, weed pollen, tree pollen, *Parietaria*, *Artemisia vulgaris*, *Aspergillus fumigatus*, *Alternaria alternata*, *Penicillium*, and cat and dog allergen extract (a solution from Allergopharma, Germany, was used in the SPT).

Allergen sIgE levels for *D. farinea*, *D. pteronyssinus*, grass pollen, weed pollen, tree pollen, *Parietaria*, and cat and dog allergen were measured by ImmunoCAP (Thermo Fisher Scientific Inc., Phadia AB, Uppsala, Sweden). SPT results were considered positive if the mean wheal diameter was 3 mm or greater; for ImmunoCAP, a positive result was defined as a value ≥ 0.35 kU/L [15, 16].

Immunotherapy

HDM and *Parietaria* pollen allergen extracts (Novo-Helisen Depot: 50% *D. pteronyssinus* + 50% *D. farinea* and Allergovit) manufactured by Allergopharma (Reinbeck, Germany) were used.

HDM allergen extract was composed of 3 vials (labeled No. 1, 2, and 3) containing 3 different concentrations of allergen (50, 500, and 5,000 therapeutic units/mL). The therapy began with subcutaneous administration of increasing doses (0.1, 0.2, 0.4, and 0.8 mL of each vial) of HDM allergen extract each week for 12 weeks, and then 1 mL of the highest allergen concentration (vial No. 3) was administered once a month as a maintenance dose.

The *Parietaria* pollen allergen extract was composed of 2 vials (labeled A and B) containing 2 different concentrations of allergen (1,000 and 10,000 therapeutic units/mL). The therapy began with subcutaneous administration of increasing doses of pollen allergen extract each week for 7 weeks and then 0.6 mL of the highest allergen concentration (vial B) was administered during weeks 6–8.

The total duration of therapy was 3 years. Common local side effects including very mild redness and swelling at the injection sites were recorded and none of the patients had significant systemic side effects.

Pharmacotherapy

Patients were treated with an eligible pharmacotherapy according to ARIA and GINA guidelines according to their needs: oral

antihistamines, intranasal corticosteroid, inhaled corticosteroid, and inhaled bronchodilator [5].

Follow-Up

The potential effect of AIT and pharmacotherapy was evaluated in patients who had been taking AIT and pharmacotherapy for at least 3 consecutive years during the follow-up period.

In the AIT group, patients were followed up weekly in the build-up phase and then monthly in the maintenance phase.

In the control group, patients' symptoms, treatment responses, and side effects of treatments were recorded 4 weeks after the start of treatment and afterwards they were followed up at 6-month intervals. However, the patients were allowed to visit additional times when necessary, such as due to a symptom increase or side effects. At the end of the third year, symptom scores, QOL scores, and medication scores were recorded for both groups.

Symptoms and Medication Scores

The symptoms scores, QOL scores, satisfaction scores, and medication scores were assessed at baseline and 3 years after the start of this study. Additionally, ACT scores and predicted FEV1% values were obtained in asthmatic patients.

The symptoms of AR were scored as follows: sneezing, nasal discharge, nasal itching, and nasal obstruction and calculated as total rhinitis symptom scores (TRSS). Patients with AR were questioned with regard to shortness of breath, cough, and wheezing, and total asthma symptom scores (TASS) were calculated. The combination of total TRSS and TASS was evaluated as the TSS [17]. Each symptom was scored as 0 (absent), 1 (mild), 2 (moderate), or 3 (severe) [18].

For perennial allergies (e.g., HDM or perennial pollen-allergic patients) the maximum score was 3 (i.e., 12 points divided by 4 nasal symptoms, with the omission of eye symptoms) [19]. For asthma, the maximum score was 3 (i.e., 9 points divided by 3 symptoms) [17]. QOL was evaluated based on QOL scores [19], satisfaction scores [20] and RAPP questionnaire scores [6]. QOL scores were evaluated with VAS scores by marking a vertical line on a 100-mm line representing severity from 0 (no symptom) to 10 (highest level of symptoms) [19]. AIT treatment satisfaction was evaluated with VAS by marking an "X" point on a line that best represented patient's current satisfaction and was assessed by means of a 100-mm horizontal VAS [20]. The RAPP questionnaire score was determined in patients with asthma and comorbid AR. For the RAPP questionnaire the maximum score was 5 (i.e., 40 points divided by 8 symptoms) [6].

The current medication use for AR with/without asthma was calculated in 4 steps with a range from 0 to 6 [20] as follows: step 0 (no need for medication), step 1 (antihistamine or leukotriene antagonists or bronchodilator), step 2 (nasal corticosteroids and inhaled corticosteroids with/without step 1 medications), step 3 (antihistamine and leukotriene antagonists and/nasal corticosteroids), and step 4 (oral corticosteroids). The level of asthma control of patients was assessed through the ACT questionnaire. According to the obtained ACT score, the patients were classified as having uncontrolled asthma (ACT score ≤ 19) or controlled asthma (ACT score > 19) [21].

Statistical Analysis

These analyses were performed using SPSS version 17 (SPSS Inc., Chicago, IL, USA).

Data are presented as means $\pm$ SD. Descriptive statistics were used to evaluate demographic and clinical characteristics. Non-parametric variables were statistically analyzed with the Wilcoxon signed rank test and the Mann-Whitney U test, and parametric variables were analyzed with a paired samples *t* test. *p* < 0.005 was considered statistically significant.

Results

Baseline Clinical Characteristics of the Patients

A total of 250 patients were included in this study. Seventy patients dropped out for the following reasons: concurrent medical problems, noncompliance, inconvenience, geographical move, or death. The drop-out rate (14.8 and 13.2% in the AIT and control groups, respectively) was approximately equal between the treatment and control groups. One hundred eighty (72%) patients completed this study (120 were in the AIT group and 60 were in the pharmacotherapy group). There were 78 males (43.33%) and 102 females (56.66%). The age range was 17–63 years (mean 36.78 ± 11.77). Ninety out of 180 patients were sensitive to HDM and 90 were *Parietaria* pollen sensitive.

One hundred twenty patients received AIT and 60 patients received antiallergic pharmacotherapy. In the first 3 months of treatment, 20 local reactions including redness and swelling at the injection sites were observed in 12 patients, whereas none of the patients had significant systemic side effects. AIT and control group patients were homogenous for clinical characteristics. Moderate-severe persistent AR was the most common type in the AIT and control groups. Thirty-four percent of the patients with AR had asthma. The prevalence of asthma or severity of asthma did not differ significantly between the AIT and control groups (*p* > 0.05).

Asthma was more frequent in patients with moderate/severe persistent AR in the IT and control groups (36%).

The TSS and QOL scores determined by the VAS and RAPP questionnaire scores, medication scores, ACT scores, and FEV1% obtained at the beginning of the AIT and pharmacotherapy were not different between the AIT and control groups (*p* > 0.05) (Table 1).

Primary Outcomes of HDM AIT, HDM Pharmacotherapy and Parietaria Pollen AIT, and Parietaria Pollen Pharmacotherapy in AR Patients with and without Asthma

The TRSS score was lower than the initial score in the AIT group after 3 years of treatment (*p* < 0.001). While there was clinical improvement for AR symptoms in the AIT group, standard pharmacotherapy did not have a sig-

Table 1. Demographics and clinical features of the patients

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7	Group 8	<i>p</i>
Patients, <i>n</i>	20	40	24	36	9	21	9	21	
Female/male ratio	17/19	18/6	24/16	8/12	11/10	5/4	12/9	7/2	0.63
Age, years	37.58±1.00 41 (20–51)	37.16±9.73 39.5 (19–55)	34.60±1.10 33 (17–62)	35.80±9.42 35.5 (19–55)	34.85±1.03 36 (21–53)	42.11±1.75 45 (16–63)	37.52±1.48 39 (18–61)	38.11±1.13 39 (21–55)	0.71
TRSS	10.61±1.47 10 (7–12)	10.37±1.55 10 (8–12)	10.50±1.60 11 (6–12)	10.20±1.54 10 (8–12)	10.04±1.62 10 (7–12)	10.33±1.58 11 (8–12)	10±1.26 10 (8–12)	10.22±1.78 10 (7–12)	0.11
TAS score		3.62±1.31 3 (1–6)		2.85±1.26 3 (1–7)		4.22±1.71 4 (2–7)		3.22±0.83 3 (2–4)	0.20
VAS scores	9.38±0.90 10 (7–10)	8.66±1.09 8 (6–10)	8.87±1.11 9 (6–10)	8.90±1.07 9 (6–10)	9.09±1.17 10 (6–10)	9.22±1.09 10 (7–10)	8.71±1.55 10 (4–10)	9.11±1.26 9 (6–10)	0.37
VAS-QOL score	9.11±0.97 9 (7–10)	8.29±1.33 9 (5–10)	8.47±1.21 9 (6–10)	8.65±1.08 8.5 (7–10)	8.95±1.24 9 (6–10)	9.11±1.05 9 (7–10)	8.90±1.44 10 (6–10)	9.25±1.38 10 (6–10)	0.36
Medication score	2.75±0.55 3 (1–4)	2.83±0.48 3 (2–4)	2.75±0.54 3 (1–4)	2.80±0.41 3 (2–3)	2.05±0.70 2 (1–3)	2.11±0.6 2 (1–3)	1.52±0.51 2 (1–2)	1.77±0.44 2 (1–2)	0.92
RAPP score	35±4.34 36 (20–40)	34±3.45 34 (22–39)	34.77±3.73 36 (21–40)	35.95±2.48 36 (30–39)	34.95±4.11 36 (28–40)	37±3.35 38 (30–40)	34±5.59 36 (20–40)	38±3.20 39 (36–40)	0.23
ACT score		20.68±1.67 21 (18–23)		20.57±2.20 20 (16–25)		21.25±1.5 21 (20–23)		21.25±2.06 21 (19–23)	0.87
FEV1%		89.16±8.54 91 (71–99)		86.31±8.67 87 (71–100)		89.33±9.01 90 (80–98)		87.33±8.08 86 (80–96)	0.32

Values are presented as means ± SD and medians (range) unless otherwise stated.

nificant impact on nasal symptoms. Additionally, QOL scores determined by VAS and RAPP questionnaire scores were lower than the initial scores in the AIT group compared to the control group ($p < 0.001$ for each score). Our results demonstrated that after 3 years the present medication use (inhaled corticosteroids, intranasal corticosteroids, and β_2 agonists) was significantly reduced in the AIT group in comparison with the control group ($p < 0.001$) Table 2.

Primary Outcomes of HDM AIT and Parietaria Pollen AIT in AR Patients with and without Asthma

TRSS, VAS symptom scores, VAS-QOL scores, medication scores, and RAPP scores were significantly decreased in both immunotherapy groups compared to the baseline scores ($p < 0.005$) (Table 3).

The improvement-of-medication score was higher in the HDM AIT group compared to the *Parietaria* pollen AIT group, but it was not statistically significant ($p > 0.05$) (Fig. 1).

Moreover, 93.3% of the patients in the HDM immunotherapy group and 78% of the patients in the *Parietaria* pollen immunotherapy group were “satisfied” with their treatment.

Primary Outcomes of HDM, Parietaria Pollen AIT, and Pharmacotherapy in AR Patients with Asthma

The data from our study showed that TAS scores and ACT scores were significantly improved in the HDM AIT group ($p < 0.001$ for each score), while they did not change in the *Parietaria* pollen AIT group compared to the control group ($p = 0.23$, $p = 0.185$).

FEV1% was increased in the third year for AIT compared to the baseline values but the difference was not statistically significant ($p = 0.225$, $p = 0.415$). FEV1% did not improve in patients receiving standard pharmacotherapy (Table 4).

Discussion

To date, there are very few studies comparing the treatment effect of AIT with pharmacotherapy for perennial AR. Matricardi et al. [24] reported on clinical efficacy in trials of AIT and trials of pharmacotherapy in patients with AR in a meta-analysis. Durham et al. [23] compared the treatment effect of sublingual immunotherapy tablets with pharmacotherapy for seasonal and perennial AR.

Table 2. Primary outcomes of HDM AIT, HDM pharmacotherapy, *Parietaria* pollen AIT, and *Parietaria* pollen pharmacotherapy in AR patients with and without asthma

	HDM				<i>p</i>	<i>Parietaria</i> Pollen				
	AIT		pharmacotherapy			AIT		pharmacotherapy		<i>p</i>
	T0	T1	T0	T1		T0	T1	T0	T1	
TRSS	10.40±1.57 10 (6–12)	3.88±2.26 4 (0–12)	10.13±1.59 10 (7–12)	8.96±2.14 9 (4–12)	<0.001	10.60±1.49 10 (7–13)	4±3.08 4 (0–12)	10.06±1.41 8 (7–12)	8.7±1.44 8 (7–12)	<0.001
VAS symptom score	8.83±1.09 9 (6–10)	2.98±1.47 3 (0–6)	9.13±1.13 10 (6–10)	8.63±1.12 8.5 (6–10)	<0.001	9.10±1.03 9.5 (6–10)	3.88±2.35 4 (0–10)	8.83±1.46 9 (4–10)	7.46±1.63 7 (5–10)	<0.001
VAS-QOL score	8.53±1.17 9 (6–10)	2.98±1.72 3 (0–9)	9.00±1.17 9 (6–10)	7.86±1.56 8 (4–10)	<0.001	8.78±1.19 9 (5–10)	3.93±2.53 3 (0–10)	9.00±1.41 10 (6–10)	5.90±1.56 5.5 (3–10)	<0.001
VAS satisfaction score		3±1.79 3 (0–9)		7.26±1.41 7 (4–10)			3.76±2.61 3.5 (0–10)		6.40±1.49 6 (4–10)	<0.001
Medication score	2.76±0.49 3 (1–4)	0.21±0.58 0 (0–3)	2.10±0.66 2 (1–3)	2.4±0.89 2 (1–4)	<0.001	2.78±0.52 3 (1–4)	0.46±0.91 0 (0–4)	1.60±0.49 2 (1–2)	2.26±0.63 2 (1–3)	<0.001
RAPP score	35.16±3.39 36 (21–40)	8.46±5.73 7.5 (2–35)	35.56±3.96 36 (28–40)	30.96±6.8 30 (18–40)	<0.001	34.60±4 35 (20–40)	11.75±8.42 10 (2–36)	35.20±5.28 38 (20–40)	31.93±3.77 32 (24–40)	<0.001
Values are presented as means ± SD and medians (range). T0, baseline; T1, 3 years after treatment.										

Table 3. Primary outcomes of HDM AIT and *Parietaria* pollen AIT in AR patients with and without asthma

	HDM AIT			<i>Parietaria</i> pollen AIT		
	T0	T1	<i>p</i>	T0	T1	<i>p</i>
TRSS	10.40±1.57 10 (6–12)	3.88±2.26 4 (0–12)	<0.001	10.60±1.49 10 (7–13)	4±3.08 4 (0–12)	<0.001
VAS symptom score	8.83±1.09 9 (6–10)	2.98±1.47 3 (0–6)	<0.001	9.10±1.03 9.5 (6–10)	3.88±2.35 4 (0–10)	<0.001
VAS-QOL score	8.53±1.17 9 (6–10)	2.98±1.72 3 (0–9)	<0.001	8.78±1.19 9 (5–10)	3.93±2.53 3 (0–10)	<0.001
VAS satisfaction score		3±1.79 3 (0–9)			3.76±2.61 3.5 (0–10)	<0.001
Medication score	2.76±0.49 3 (1–4)	0.21±0.58 0 (0–3)	<0.001	2.78±0.52 3 (1–4)	0.46±0.91 0 (0–4)	<0.001
RAPP score	35.16±3.39 36 (21–40)	8.46±5.73 7.5 (2–35)	<0.001	34.60±4.0 35 (20–40)	11.75±8.42 10 (2–36)	0.032

Values are presented as means ± SD and medians (range). T0, baseline; T1, 3 years after treatment.

According to their study, the effect sizes of pharmacotherapies for perennial AR were approximately 1.5–2 times less than that observed for seasonal AR, although the effect sizes of sublingual immunotherapy tablets were almost the same for seasonal and perennial AR [23].

To our knowledge, this is the first randomized controlled real-life observational study comparing HDM and *Parietaria* pollen AIT with pharmacotherapy to examine the efficacy in AR patients with/without asthma 3 years after the start of treatment.

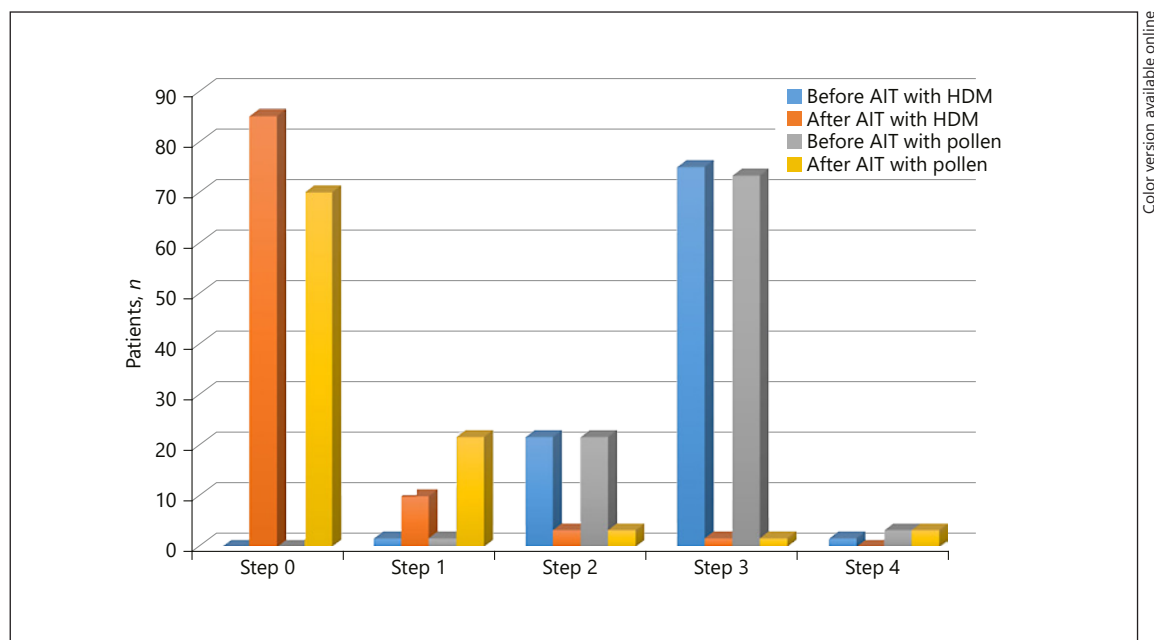


Fig. 1. Frequency of medication before and after HDM and pollen AIT.

Evaluation of the clinical efficacy of immunotherapy includes measurement of nasal symptoms scores, QOL scores, and medication scores [10].

The power of this study is that various evaluation parameters such as TSS, VAS-QOL scores, VAS satisfaction scores, medication scores, RAPP questionnaire scores, medication use scores, ACT scores, and FEV1% measurements were used in conjunction.

Data from the literature showed that AIT had a greater mean relative clinical effect for reducing nasal symptoms than pharmacotherapy [24]. Purkey et al. [25], who analyzed data from 12 randomized controlled trials, reported an important decrease in AR symptom scores. Additionally, in a recent study Feng et al. [26] showed that immunotherapy-treated patients had lower rhinitis symptom scores.

This study demonstrated that there was clinical improvement in AR symptoms in the immunotherapy group, whereas standard pharmacotherapy had no significant effect on nasal symptoms. Similarly AIT was more effective on asthma symptoms compared to pharmacotherapy.

Ciprandi et al. [25] suggested that patient's perception of symptom severity assessed by a VAS may be a practical approach to assess AIT efficacy. Droessaert et al. [28] assessed the level of symptom control using a VAS for total nasal symptoms and other clinically important parameters

like severity and duration of symptoms and medication use in the patient population that had been started on either pharmacotherapy or AIT 3 years prior to the study. The results of their study showed that the majority of patients who had undergone AIT performed better in terms of symptom control, severity of disease, and medication use [28].

In our study, the QOL and satisfaction scores evaluated with a VAS showed improvement compared to the pharmacotherapy group ($p < 0.001$). Furthermore, patients in the HDM AIT group were more satisfied with the AIT.

In a recent study, Molinengo et al. [29] reported that RAPP met all of the criteria to be considered a reliable and valid health-related QOL measure in patients with asthma and comorbid AR in practice.

Until now, there has been no study on the evaluation of AIT efficacy based on the RAPP parameter in clinical practice. In this study, for the first time RAPP questionnaire scores were assessed and compared before and after treatment among AR patients with/without asthma. Consequently, 3 years after the beginning of treatment, in the AIT group RAPP questionnaire scores significantly decreased compared to the pharmacotherapy group ($p < 0.001$).

Some studies have shown that subcutaneous immunotherapy decreases medication use in patients with AR/asthma [30]. A systematic review by Purkey et al. [25]

Table 4. Change in asthma scores after AIT or pharmacotherapy

	HDM AIT with asthma		HDM pharmacotherapy with asthma		<i>p</i>	<i>Parietaria</i> pollen AIT with asthma		<i>Parietaria</i> pollen pharmacotherapy with asthma		<i>p</i>
	T0	T1	T0	T1		T0	T1	T0	T1	
TAS score	3.62±1.31 3 (1–6)	1.54±0.83 1.5 (0–3)	2.85±1.26 3 (1–7)	5.55±2.12 6 (2–9)	<0.001	4.22±1.71 4 (2–7)	1.10±1.07 1 (0–4)	3.22±0.83 3 (2–4)	3.6±1.93 5 (0–5)	0.23
ACT score	20.68±1.67 21 (18–23)	24.05±1.13 24 (21–25)	21.25±1.5 21 (20–23)	20±1.41 20 (18–21)	<0.001	20.57±2.20 20 (16–25)	22.71±2.75 24 (15–25)	21.25±2.06 21 (19–23)	19.75±1.5 20 (18–21)	0.185
FEV1%	89.16±8.54 91 (71–99)	95.33±5.63 96.5 (84–100)	89.33±9.01 90 (80–98)	86.66±9.04 86 (78–96)	0.225	86.31±8.67 87 (71–100)	89.03±7.42 87 (75–100)	87.33±8.08 86 (80–96)	83.66±7.37 81 (78–92)	0.415

Values are presented as means ± SD and medians (range). T0, baseline; T1, 3 years after treatment.

proposed that subcutaneous immunotherapy for AR significantly improved medication scores and is recommended for patients with seasonal or perennial AR. Similarly our results demonstrated that AIT for AR improved medication scores.

There are several studies of AIT which have demonstrated improvement in asthma symptoms [22, 31]. The strongest evidence for asthma symptom improvement was reported in a meta-analysis by Abramson et al. [32]. This meta-analysis showed significant improvement in asthma symptoms scores [32]. Additionally, a double-blind placebo-controlled study showed that HDM immunotherapy was effective in improving symptom control in Chinese patients with mild to moderate allergic asthma [23]. Similarly, according to our results AIT with HDM improved TASS and ACT scores compared to standard pharmacotherapy ($p < 0.001$).

A weakness of our study is that the number of patients assigned to HDM pharmacotherapy with asthma and *Parietaria* pollen pharmacotherapy with asthma was small.

Patients with moderate to severe asthma showed no improvement with AIT in a study by Polzehl et al. [33].

In our study AIT with *Parietaria* pollen did not change asthma symptom scores at the end of 3 years of therapy. This was concordant with the results of 3 years of grass pollen AIT in another study [11].

Some studies have revealed that FEV1% improves significantly in patients receiving AIT compared with those in the control group who do not receive AIT [23, 34].

On the contrary another report showed no statistical significance in FEV1% between the subcutaneous immunotherapy and control groups [35].

In our study FEV1% was increased compared with the baseline value in the AIT group, but it was not statisti-

cally significant ($p > 0.05$). On the other hand, FEV1% remained without any improvement in patients on standard pharmacotherapy.

Conclusion

Perennial AIT was found superior to pharmacotherapy in decreasing symptoms as well as in improving QOL scores in AR patients with/without asthma. HDM AIT was more effective for asthma symptoms than *Parietaria* pollen AIT.

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Statement of Ethics

Informed consent was obtained from all of the patients and this study was approved by the Institutional Review Board of the Istanbul Education and Research Hospital. (approval identification No. 1718).

Disclosure Statement

The authors declare that they have no conflict of interests.

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