АЛЛЕРГЕН-СПЕЦИФИЧЕСКАЯ ИММУНОТЕРАПИЯ СНИЖАЕТ КЛИНИЧЕСКИЕ ПРОЯВЛЕНИЯ АЛЛЕРГИЧЕСКОГО РИНИТА

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Резюме. Распространенность аллергических заболеваний, включая ринит и аллергическую астму, растет в современном мире, что можно объяснить «теорией гигиены». Избегание воздействия аллергенов и лекарственная терапия для облегчения клинических симптомов у этих пациентов недостаточны и малоэффективны. В настоящее время единственным стабильным методом лечением считается аллерген-специфическая иммунотерапия. Предыдущие исследования в Иране в некоторой степени касались эффективности этого лечения, однако при этом не проводилось дальнейшее наблюдение за состоянием пациентов, как в плане клинического улучшения, так и побочных эффектов, и в настоящем исследовании мы рассматривали эти вопросы одновременно. После получения информированного личного согласия для выбранных пациентов была заполнена стандартная форма анкеты в соответствии с условиями включения в исследование. Результаты были проанализированы с помощью статистической программы SPSS. В настоящем исследовании участвовали 64 пациента в возрасте 34,5 (±10,5) года; в том числе 25 женщин. Иммунотерапия против деревьев, травы, сорняков и клещей была проведена соответственно, у 57, 49, 53 и 1 пациентов. Медианный (межквартильный) балл по астме у этих людей до и после иммунотерапии составил 8 (5-9) и 2 (1-3) соответственно. После иммунотерапии отмечено значительное снижение оценок в баллах по симптомам астмы, наличию хрипов, одышки и кашля у исследуемых субъектов ($p < 0,0001$ в общей группе). Медианный (межквартильный) балл по аллергическому риниту у этих людей до и после иммунотерапии составил 16 (12-20) и 2 (1-4) соответственно. Оценки по симптомам аллергического ринита – чиханию, насморку, назальному зуду, заложенности носа, зуду в глазах, слезотечению и покраснению глаз у этих пациентов значительно снизились после иммунотерапии ($p < 0,0001$ для всех случаев). Местные, распространенные и системные осложнения были зарегистрированы в 10, 2 и 3 случаях соответственно. Это исследование показало, что стандартная иммунотерапия с использованием обычных нативных аллергенов может улучшить значительные клинические симптомы у пациентов с умеренным или тяжелым аллергическим ринитом и легкой или умеренной аллергической астмой, которые не отреагировали адекватно на медикаментозное лечение. Для этих пациентов можно применить данный эффективный метод лечения.

Ключевые слова: специфическая иммунотерапия, аллергический ринит, астма

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ALLERGEN SPECIFIC IMMUNOTHERAPY ATTENUATES ALLERGIC RHINITIS CLINICAL MANIFESTATIONS

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Abstract. The prevalence of allergic diseases, including rhinitis and allergic asthma, is increasing in the modern world based on the Hygiene theory. Avoidance of allergens and using drugs to relieve clinical symptoms in these patients are not sufficient and efficient. Currently, allergen-specific immunotherapy is the only stable treatment approach. Previous studies in Iran have investigated the efficiency of this treatment. However, they had not performed a simultaneous follow-up of treatment status, with respect to patients' recovery and side effects. In the present study, we addressed these issues together. After obtaining informed personal consent, a standard questionnaire form was completed for the selected patients according to the study's entry conditions. The results were analyzed using SPSS, a statistical software program. Of the 64 patients in the present study with an average age of 34.48 (±10.46) years, 25 were women. Immunotherapy against antigens from trees, grass, weeds, and mites was performed, respectively for 57, 49, 53, and 1 allergy cases in the study, The median (IQR) asthma score in these persons before and after immunotherapy was 8 (5-9) and 2 (1-3), respectively. After immunotherapy, the scores of asthma, wheezing, shortness of breath, and cough in the studied subjects were shown to be significantly decreased ($p < 0.0001$ for entire group). The median (IQR) score of allergic rhinitis in these people before and after immunotherapy was 16 (12-20) and 2 (1-4), respectively. The scores of allergic rhinitis, sneezing, runny nose, nasal itching, nasal congestion, itchy eyes, watery eyes, and red eyes in these patients were significantly decreased after immunotherapy ($p < 0.0001$ for the total group). Local, extensive, and systemic complications were reported in 10, 2, and 3 cases, respectively. This study demonstrated that standard immunotherapy using common native allergens can improve significant clinical symptoms in patients with moderate to severe allergic rhinitis and mild-to-moderate allergic asthma who have not responded adequately to conventional therapy. An effective treatment approach should be suggested for these patients.

Keywords: specific immunotherapy, SCIT, allergic rhinitis, asthma

Introduction

Allergic rhinitis is an atopic disorder that can involve the nose and cause the following symptoms: itching, rhinorrhea, sneezing, and nasal congestion. In addition, some other parts of the body, such as the eyes, throat, and ears, may also be affected by allergic rhinitis. Allergies account for around 50% of all cases of rhinitis [1]. The global prevalence of allergic rhinitis is steadily increasing, affecting more than 400 million people [2, 3]. Atopic disorders can lead to higher healthcare expenses, particularly for individuals with uncontrolled or poorly managed allergies [4, 5]. AR is strongly associated with common allergens, so it can be prevented to some extent by avoiding allergens and using special medicinal agents. Still, changing the course of allergic diseases related to allergens is difficult [3].

Patients with allergic rhinitis should avoid allergens that trigger their symptoms. For mild intermittent and mild persistent allergic rhinitis, the first-line treatment may include a second-generation H1 antihistamine (such as cetirizine, fexofenadine, desloratadine, or loratadine) or an intranasal antihistamine (such as azelastine or olopatadine). Patients experiencing ongoing moderate to severe allergic rhinitis should initially be treated with an intranasal corticosteroid (such as fluticasone, triamcinolone, budesonide, or mometasone), either alone or in combination with an intranasal antihistamine [6].

Allergen-specific immunotherapy (AIT) is the only method capable of changing the course of allergic diseases. Compared to pharmacological therapeutic agents that relieve most symptoms, AIT has advantages: 1. It prevents sensitization to new allergens, 2. It reduces the likelihood of asthma, and 3. It can maintain the therapeutic effects if the treatment course is completed [7, 8]. Several studies have proven the significant effectiveness of AIT in reducing symptoms and the need for drug treatments in patients with allergic rhinitis [9, 10].

Previous studies have shown the greater effectiveness of subcutaneous immunotherapy (SCIT) despite its more adverse systemic side effects than sublingual immunotherapy [11, 12]. Several studies have been conducted to regulate the therapeutic effects of SCIT and reduce possible side effects [13]. The clinical results of AIT differ from one patient to

another according to ethnicity (genetic differences), climate, and especially the significant allergens of their place of residence. In addition, biomarkers and predictive clinical parameters in response to AIT treatment are still poorly defined [14].

Previous studies in Iran have investigated the effectiveness of this treatment to some extent. However, they had not studied the follow-up of the treatment status in terms of patients' recovery and side effects at the same time, and in the present study, we addressed these issues simultaneously. This study could provide valuable insights applicable to other populations and influence treatment protocols and related policies. Therefore, the present study was designed to investigate the clinical outcomes and side effects of SCIT in the Iranian patient population in AR and asthma and their symptoms.

Materials and methods

All procedures were performed under ethical principles, and patients consented by filling out a written form. The results were considered confidential, and no costs were imposed on the patients.

To obtain the number of samples, we considered the p-value to be less than 0.05 and the percentage of error equal to 0.1. According to previous studies, we thought the possibility of immunotherapy's effect on allergic rhinitis and asthma symptoms to be 70% and its non-effect to be 30%. Based on this, we needed at least 60 patient samples. Since the treatment was long and it was expected that several patients would withdraw from the treatment, the initial sample was selected in larger numbers [15].

Inclusion criteria

In this prospective cohort study, patients with AR aged 5-65 years who visited the Asthma and Allergy Clinic of Dr. Masih Deneshvari Hospital from 2016-2022 and were confirmed to be atopic and allergic by history, physical examination, and positive prick test of common allergens (Tree, grass, weed, and mite) were included in this study. Induration and erythema over 3 mm are considered positive prick tests.

Exclusion criteria

Patients with the diagnosis of advanced/worsening or non-controlled asthma, active autoimmune disease, pregnancy, immunodeficiency disease, malignant tumors (which are absolute contraindications of SCIT), and taking beta-blocker drugs (relative contraindication of SCIT) before or during the treatment were excluded [2]. Patients not visiting regularly or withdrawing from treatment were also not included.

For included patients, general profile, asthma, and AR symptoms scores (according to GINA and ARIA guidelines), medicinal agents, and side effects associated with immunotherapy (local, large local, and systemic) were collected before and after SCIT.

A total of 253 patients with symptoms of allergic rhinitis were referred to Masih Daneshvari Hospital's Asthma and Allergy Clinic (a tertiary center), of which 98 cases were included in the study based on history, clinical examination and positive prick test. Among them, 34 patients did not continue the treatment and were excluded from the study. Finally, 64 patients completed all treatment stages. Final patients underwent the conventional schedule of immunotherapy with allergen extract (Stallergen Greer Company, USA) with three vials of Dilutions of 1:1000 picograms (pg) were applied every week for ten sessions, 1:100 pg every other week for ten sessions, and then with 1:10 pg dilutions at an interval of one month for 2-3.5 years. The therapeutic doses of 0.05 ml as a subcutaneous injection from a 1:1000 vial were administered and continued with a fixed dose of 0.5 ml from a 1:100 vial until the end of the treatment period [16].

Patients were warned about the side effects of these injections both in written personal consent and verbally. Side effects are possible, but not everyone will experience them. Severe reactions are uncommon. Most reactions are limited to the injection site and include redness, swelling, itching, and pain. It was explained to the patients that if these local side effects bother them, they can use a topical antihistamine until the symptoms disappear. Patients were closely monitored due to the risk of severe reactions, including anaphylaxis, for at least 3 hours in the clinic on an outpatient basis, and their vital signs were observed and recorded. All patients were given the doctor's number so they could contact them in case of delayed complications, and they were advised to call the local ambulance number in case of any acute and severe symptoms such as chest pain, shortness of breath, and decreased level of consciousness.

From the day of injection to three days after, patients were advised to avoid vigorous physical activity and hot baths because these activities can increase the possibility of delayed reactions.

Analysis was conducted using SPSS version 16.0 (SPSS, Inc. Chicago, USA) and GraphPad Prism software (version 6; 07 GraphPad Software, Inc.). Non-parametric Chi-Square and Mann-Whitney U Test (median) were used for the non-normally distributed variables, and a One-way ANOVA (mean±SD) was used for normally distributed variables. We conducted correlation analysis using the Spearman Correlation Test. P-values < 0.05 were considered as statistically significant.

Results

Of 98 patients with allergic rhinitis symptoms referred to Masih Daneshvari Hospital's Asthma and Allergy Clinic, 34 were excluded because they did not

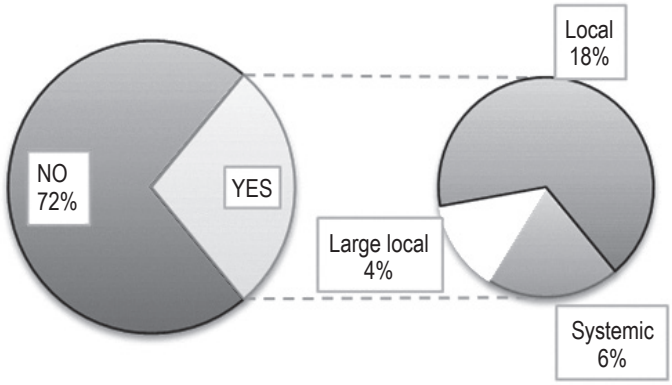

Figure 1. Distribution of side effects of immunotherapy in the studied population

visit regularly or withdrew from treatment due to a long treatment period.

Of 64 included AR patients, 15 had side effects following immunotherapy (Figure 1). Local, large local, and systemic complications were reported in 10, 2, and 3 cases, respectively. Local side effects (local or large local) included itching, swelling, and redness at the injection site, for which the patients were given topical antihistamines. Three of the patients had systemic complications in the exact first injection. This complication was not repeated in other injections. All three patients had cutaneous, gastrointestinal, or respiratory symptoms at the same time, and they were immediately injected with intramuscular epinephrine and then treated with systemic antihistamines and prednisolone. The next injection was given ten times diluted for these patients but at the same interval. None of the patients suffered severe anaphylaxis.

Of 64 patients included in the present study aged 34.48 (±10.46) years (age range: 14-59 years), 25 cases were women (39.68%). The median (IQR) age of onset of symptoms and the age of diagnosis were 15 (10-26) and 25 (18.25-30) years, respectively. Allergen immunotherapy against trees, weeds, grass, and mites was performed for 57, 49, 53, and 1 of the subjects, respectively. Immunotherapy against 1, 2, and 3 allergens was performed for 8, 4, and 48 patients, respectively, and the types were not specified in 4 patients.

No significant difference was reported between the groups based on the number of allergens in asthma and allergic rhinitis scores after allergen immunotherapy ($p = 0.667$ and 0.563, respectively). 36, 12, and 29 cases reported a history of eczema, asthma, and food allergy. About 74% of the patients' families had a history of allergic diseases.

The median (IQR) asthma score of patients before immunotherapy and after immunotherapy was 8 (5-9) and 2 (1-3), respectively. After immunotherapy, the scores of asthma, wheezing, shortness of breath, and cough of subjects significantly decreased ($p < 0.0001$ all) (Figure 2).

In 5 cases (of 12 with simultaneous asthma and AR), complete asthma recovery was reported after the completion of immunotherapy. The need to use common drugs to treat asthma in these people was significantly reduced, which is clinically significant. However, this difference was not statistically significant, likely due to the small number of people ($p = 0.083$).

The AR median (IQR) score of allergic patients before and after allergen immunotherapy was 16 (12-20) and 2 (1-4), respectively. The scores of AR, sneezing, runny nose, itchy nose, nasal congestion, itchy eyes, watery eyes, and eyes redness of patients significantly decreased after immunotherapy ($p < 0.0001$ all) (Figure 3).

All participants except one were treated with common medicinal agents for AR. Among the 64 patients with AR, about 20% ($n = 13$) were cured entirely after immunotherapy (AR score = 0). The need to prescribe common drugs in the treatment of AR after immunotherapy showed a statistically significant decrease (Table 1).

TABLE 1. USE OF COMMON DRUGS IN THE TREATMENT OF ALLERGIC RHINITIS

Type of drugs		Yes (n/63)	p value
Oral H1-antihistamine	Before After	61 22	< 0.0001*
Intranasal H1-antihistamine	Before After	1 1	1.000
Intranasal corticosteroids	Before After	40 17	< 0.0001*
Prednisolone	Before After	13 1	0.001*

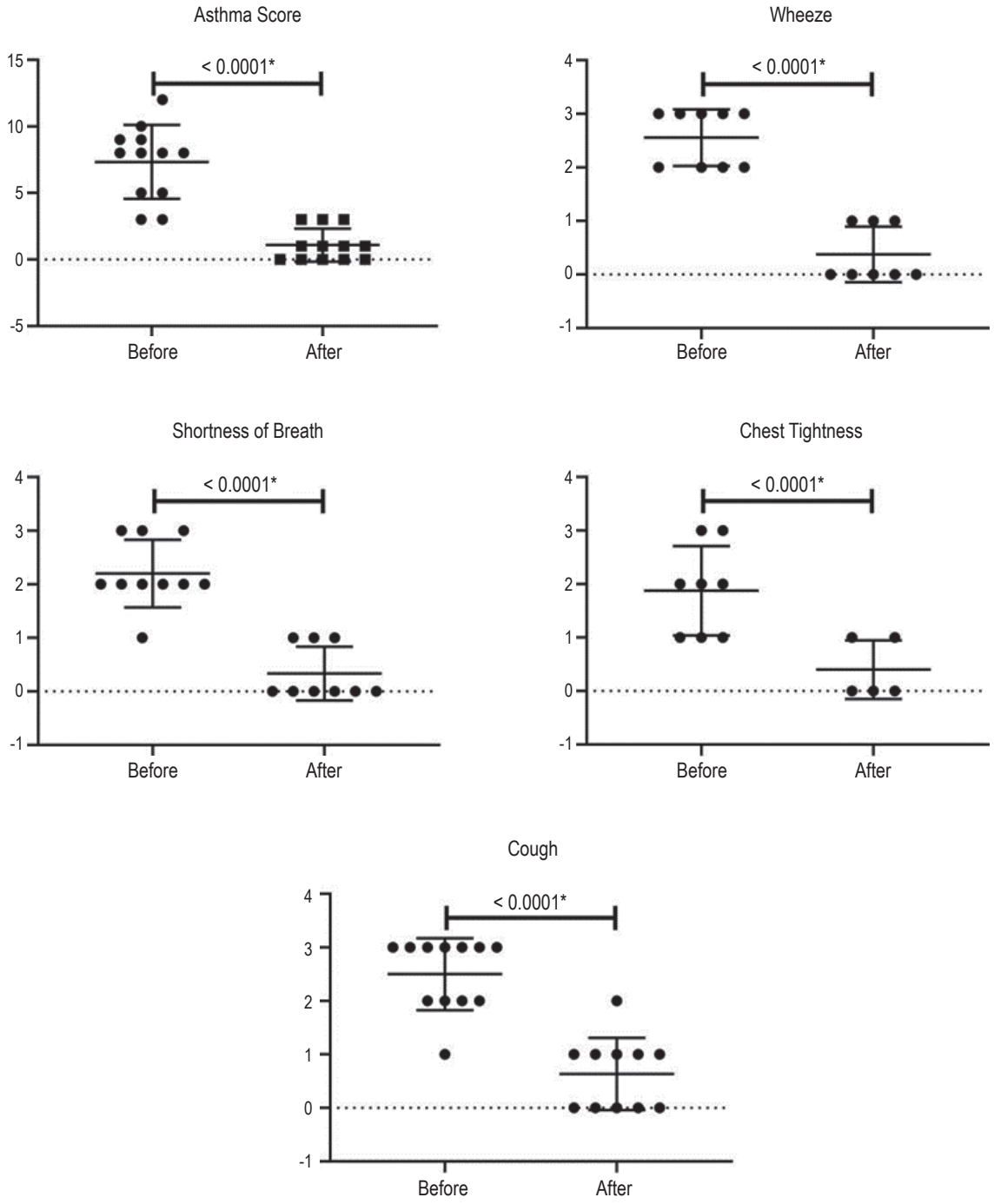

Figure 2. Scoring of asthma and its symptoms

Note. Asthma and related symptoms, including wheezing, shortness of breath, chest tightness, and cough, scored from 0 (no symptom) to 4 (worst). P-values < 0.05 were considered as statistically significant.

Classification of people based on age (10-20, 20-30, 30-40, 40-50, and 50-60 years old) showed no significant difference in asthma and rhinitis scores before and after immunotherapy (asthma before immunotherapy p = 0.098, asthma after immunotherapy p = 0.646, rhinitis before immunotherapy p = 0.668 and rhinitis after immunotherapy p = 0.820). The classification of people based on gender also was indicative of no significant difference in asthma and rhinitis scores before and after immunotherapy (asthma before immunotherapy p = 0.583, asthma after immunotherapy p = 0.147, rhinitis before immunotherapy p = 0.435 and rhinitis after immunotherapy p = 0.440).

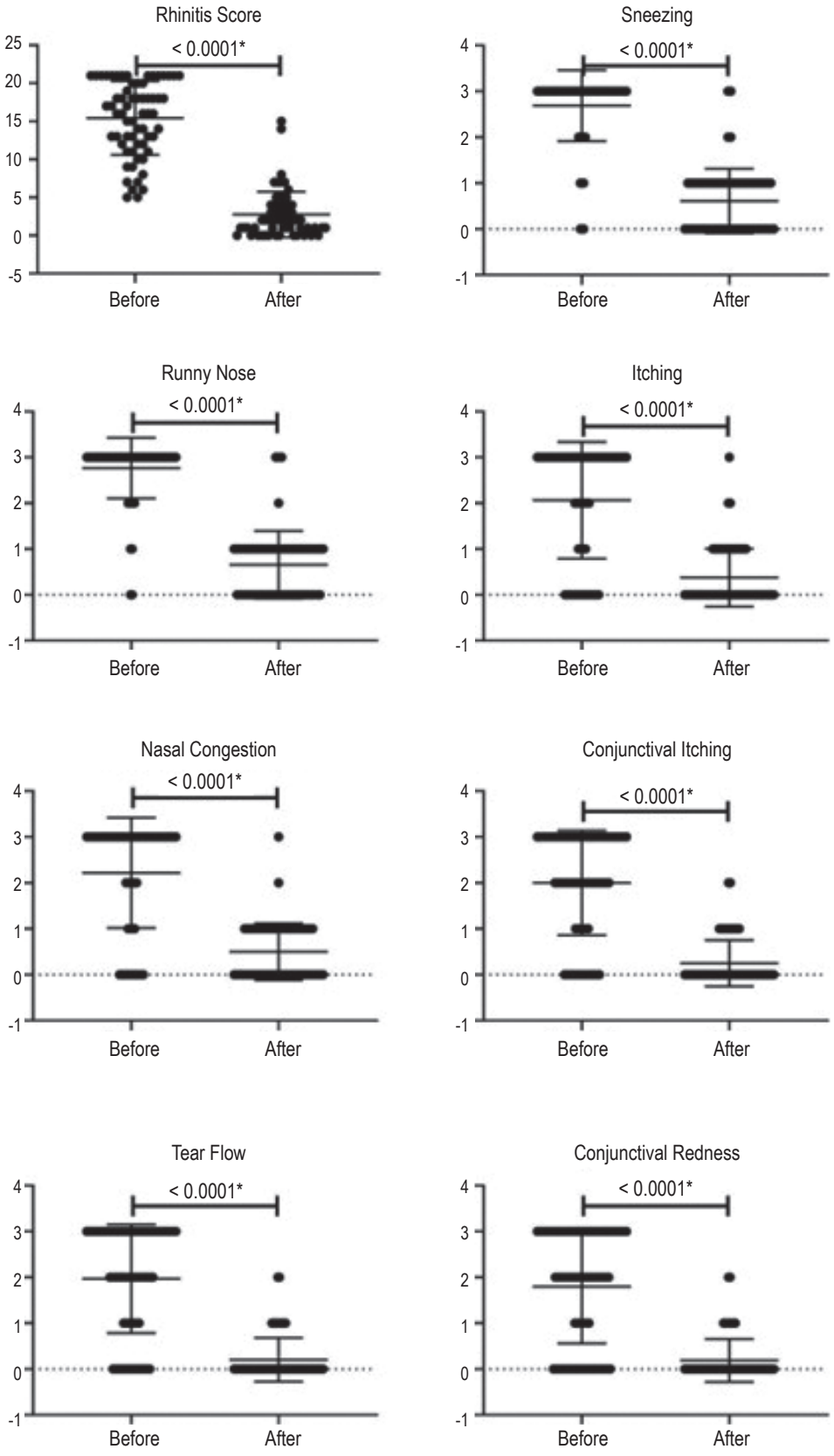

Figure 3. Allergic rhinitis scoring and its symptoms

Note. AR and related symptoms, including sneezing, runny nose, itching, nasal congestion, conjunctival itching, tear flow, and conjunctival redness, scored from 0 (no symptom) to 4 (worst). P-values < 0.05 were considered as statistically significant.

Discussion

The study was somewhat limited due to its long duration, resulting in some loss of information for certain patients. This study aimed to investigate the effects of subcutaneous immunotherapy on clinical symptoms related to allergic rhinitis in 64 patients with an average age of 34.48 (±10.46) years, 60.32% of whom were male. The median (IQR) age at which symptoms began was 15 (10-26) years, and the median (IQR) age at which the disease was diagnosed was 25 (18.25-30) years. Some studies have indicated that allergic rhinitis is more commonly reported in males before puberty, but it is uncertain whether a similar gender predominance persists after puberty [17]. However, similar to the present study's findings, Nafee et al. reported the predominance of males in adults with AR [18]. In this regard, longitudinal studies must confirm these cross-sectional data and examine the determining factors and underlying mechanisms.

Based on a report from the European Academy of Allergy and Clinical Immunology (EACCI) in 2017, allergic rhinitis (AR) is a systemic allergic disorder that is primarily linked to various conditions such as asthma, eczema, food allergies, eosinophilic esophagitis (EoE), conjunctivitis, rhinosinusitis, adenoid hypertrophy, olfactory disorders, and obstruction [19]. The latest research has confirmed a connection between asthma and adult rhinitis. Out of 64 patients with allergic rhinitis (AR) in the current study, 36 had a history of eczema, 29 had a history of food allergy, and 12 had a history of asthma. Similarly, in a previous study on the co-occurrence of AR and eczema, Lee et al. found eczema to be the most common atopic disease in AR subjects [20]. A high prevalence of allergic rhinitis (AR) in patients with asthma was reported, affecting up to 89.5% of individuals. [21]. In addition, poor asthma control association was reported with rhinitis, smoking, and low medication adherence [22]. The study found that treating AR effectively can lead to improved recovery and treatment of asthma. The median (IQR) asthma score in the subjects before [8 (5-9)] and after [2.00 (1-3)] immunotherapy was reported in the study. It was also noted that 5 out of 12 subjects with asthma and AR experienced complete asthma remission after immunotherapy. Furthermore, treating grass pollen AR patients with immunotherapy improved their quality of life during allergy season and reduced seasonal asthma and bronchial hypersensitivity symptoms [23]. This connection can be explained by the pathophysiological link between allergic rhinitis (AR) and asthma.

The median (IQR) score of AR before and after immunotherapy was 16 (12-20) and 2 (1-4), respectively. After immunotherapy, the scores for AR, sneezing, runny nose, itchy nose, nasal congestion, itchy eyes, and watery and red eyes of patients significantly decreased ($p < 0.0001$ in all cases) (see Figure 3). Likewise, Kozegran et al. observed improvements in the clinical symptoms of moderate to severe AR patients after SCIT [24]. A simultaneous decrease in IFN gamma, IL4, GITR, and FOXP3 accompanied elevated serum TGF beta and IL10 levels. Interestingly, there was a significant decrease in the prescription of standard drugs for AR (as shown in Table 1), and 20% of patients ($n = 13$) showed complete recovery from AR (AR score = 0) after receiving immunotherapy. This contrasts with a previous study by Zandkarimi et al., which reported complete recovery in 70% of patients [15]. This difference emphasizes the need for further studies and assessing markers associated with allergies.

The potential benefits of immunotherapy should be carefully considered in light of the rare but severe risks of systemic allergic reactions and fatal anaphylaxis. A national survey of allergists in North America between 1990 and 2001 found an average of 3.4 fatal reactions per year, amounting to one fatal reaction in every 2.5 million visits for immunotherapy injections [25]. Adverse allergic reactions to subcutaneous immunotherapy (SCIT) are classified as local or systemic reactions. Large local reactions (LLRs) are defined as pruritus and/or erythema (greater than 2.5-3 cm) at the injection site and are common among recipients. In the current study, out of the 64 patients with allergic rhinitis who participated in the research, only 15 reported experiencing side effects following immunotherapy. Of these, 10 cases reported local complications, 2 reported large local complications, and 3 reported systemic complications.

According to a 2013 study by the American Academy of Allergy, Asthma & Immunology (AAAAI), the rate of systemic reactions related to SCIT is relatively low, ranging from 0.1% to 0.2% [26], and about 26-86% of patients who received SCIT they experience local reactions [27, 28]. Known risk factors for fatal reactions include uncontrolled asthma at the time of injection, incorrect dose, delayed administration or inadequate administration of epinephrine during anaphylaxis, previous history of systemic injection-related reactions, and injections administered during peak allergy seasons [25, 29].

Allergen immunotherapy involves gradually administering increasing amounts of allergen extract, with the goal of reaching an optimal "maintenance dose" within the range of concentrations previously shown to be clinically effective for a specific allergen therapy. This method has been used effectively for decades in clinical practice to treat patients with

allergic rhinitis, allergic asthma, and anaphylaxis to insect bites. Immunotherapy with allergens is a slow treatment that alters the disease's immunological mechanisms. A meta-analysis comparing the therapeutic effects of subcutaneous immunotherapy and common medications has shown that immunotherapy has similar effects to drug therapy and may even be considered in future developments [30].

Conclusion

The current study's results showed that if essential immunotherapy is performed in the right patient, it will be an effective and safe treatment that not only prevents symptoms but also aids in preventing the progression of the disease and can reduce the severity of the disease. Moreover, immunotherapy in patients with AR caused significant improvement in allergic asthma.

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Ethics approval

The institutional review board of ethics of Shahid Beheshti University of Medical Sciences approved the study protocol with reference number IR.SBMU.MSP.REC.1400.385. All participants signed written informed consent. The trial investigator explained the study's aims, advantages, and possible side effects to eligible patients. Patients were told that they were free to withdraw from the study at any time before the injections.

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