ACH Med J
(2024) 3: 112-117
ISSN:2822-5872
Doi : 10.5505/achmedj.2024.03016

RESEARCH ARTICLE

Effect of specific immunotherapy on plasma interleukin 13 and 8 levels in patients with allergic rhinitis

Gulsen Duman Talas,[1] Goksal Keskin[2]
[1]Internal Medicine, Ankara Bilkent City Hospital, Ankara, Turkiye
[2]Department Of Internal Medicine, Division Of Immunology And Allergy, Ankara University Faculty Of Medicine, Ankara, Turkiye

Article Info

Received Date: 10.07.2024
Revision Date : 25.09.2024
Accepted Date: 25.09.2024

Keywords:
Allergic rhinitis,
İmmunotherapy,
IL-13,
IL-8 .

ORCIDs of the authors:
GDT: 0009-0001-6903-0051
GK : 0000-0001-8553-5378

Abstract

Introductıon: This study aimed to evaluate interleukin (IL)-13 and IL-8 levels in patients with allergic rhinitis who were and were not receiving specific immunotherapy.

Methods: A total of 84 patients being followed up in the immunology-allergy outpatient clinic for allergic rhinitis (42 receiving immunotherapy) and 23 healthy control subjects were included. Serum IL-13 and IL-8 levels were measured by enzyme-linked immunosorbent assay in all groups. Allergic rhinitis patients were also evaluated in terms of symptom scores, IgE levels, and skin prick test results.

Results: Comparison of serum IL-13 and IL-8 among the groups demonstrated that levels of both cytokines were significantly higher in both allergic rhinitis patient groups compared to controls ($p<0.001$), and significantly higher in symptomatic allergic rhinitis patients compared to patients receiving immunotherapy ($p<0.001$ for IL-13, $p=0.004$ for IL-8).

Conclusion: Immunotherapy is the only curative treatment for allergic rhinitis. The results of our study suggest that immunotherapy exerts its effect by modifying levels of IL-13 and IL-8 in addition to previously well-known cytokines.

Correspondence Address: Üniversiteler Mahallesi 1604. Cadde No: 9 Çankaya Ankara - Türkiye
Phone: +90 543 760 57 30/ **e-mail:** gulsenduman78@hotmail.com

Introduction

Allergic rhinitis is one of the most common chronic diseases, affecting 10-40% of the entire population. Epidemiological data demonstrate an increase in its prevalence.[1,2] Although generally not a severe disease, it reduces quality of life and causes significant financial and labor loss.

Allergic rhinitis affects the nasal cavity and paranasal sinuses, manifesting as a complex of symptoms that includes sneezing attacks, itching of the nose and palate, rhinorrhea, and nasal congestion. Other symptoms such as eye itching and watering, postnasal discharge, decreased hearing, cough, and shortness of breath may also occur.[3,4]

As allergic rhinitis is a disease of atopic individuals, these patients may also have systemic allergic symptoms. The cause is an IgE-dependent type 1 hypersensitivity reaction, and symptoms occur as a result of the person's previous exposure to the IgE-inducing allergen. The IgE antibodies bind to receptors on mast cells in the respiratory mucosa and basophils in the peripheral circulation. Cross-linking of allergens to the IgE antibodies on the surface of these cells results in mast cells releasing preformed chemical mediators. These cells also produce other mediators and cytokines that cause the development of chronic symptoms due to nasal inflammation and continuous allergen exposure.[5,6]

Cytokines are regulatory proteins secreted by cells involved in both the specific and innate immune systems and are vital for immune system functions. Although cytokines are not antigen-specific, their production and secretion are dependent on antigen stimulation. They have different names because they originate from many different cells and exert different effects on different target cells.

Cytokines play a role in all stages of immune response and inflammation, including antigen presentation, immune cell differentiation, maturation, and activation, adhesion molecule expression, and acute phase response.[7,8] They also play an important role in the pathogenesis of allergic diseases. Based on these characteristics, in this study we examined changes in serum levels of the cytokines interleukin (IL)-8 and IL-13 in patients with allergic rhinitis who did and did not receive specific immunotherapy (SIT).

Material and Methods

The study included patients who presented to the immunology/allergy outpatient clinic in the internal medicine department of the Ministry of Health Dışkapı Training and Research Hospital and were diagnosed with allergic rhinitis by history, physical examination, laboratory, and skin tests. The patients were grouped into those who were not receiving SIT and were symptomatic (Group 1, n=42) and those who were receiving SIT (Group 2, n=42). The control group included healthy individuals with no known systemic diseases who were shown to have no allergic disease according to history, physical examination, and skin tests (n=23). The study was approved by the Ethics Committee of Dışkapı Yıldırım Beyazıt Training and Research Hospital, with the approval number 33/2009 and the date 19.03.2009.

Inclusion criteria; Patients aged ≤45 years diagnosed with allergic rhinitis by history, physical examination, laboratory, and skin tests. Healthy individuals aged ≤45 years were included in the control group. Exclusion criteria: Individuals with systemic diseases other than allergic rhinitis or those with incomplete clinical data were excluded from the study.

Morning fasting blood samples were collected from all subjects for measurement of IL-13, IL-8, and IgE levels. Serum was separated and stored at -70°C until analysis.

Skin prick tests with 48 allergens, including common aeroallergens (Stallergenes, In Vitro Allergy Diagnosis Kit, France), were performed on the forearm using standard needles with a 1.0-mm tip. Physiological saline solution was used as the negative control and 10 mg/mL histamine solution was used as the positive control. The results were evaluated after 15 minutes, and a wheal 10-15 mm in diameter (grade 3+) was accepted as a positive reaction.

In clinical trials for the treatment of allergic rhinitis, patients are often asked to keep a daily log of complaints and their severity. Considering that symptoms may differ between day and night, an extended symptom scoring format including nighttime symptoms (such as difficulty falling asleep, frequent waking) was used. In this scoring system, symptoms are rated by severity as none,⁰ mild but not disturbing.¹ moderate and occasionally disturbing,² severe and often disturbing.³ The symptom scores of our patients were assessed and recorded in follow-up visits.

eStallergenes APSI allergen extracts (France)

were administered as SIT. Injections were initially performed weekly. After reaching a certain dose (maintenance dose), this interval was extended to once every 15 days and later to once a month. Injections were administered subcutaneously over the deltoid muscle.

Serum IL-13 and IL-8 levels of the patients and control subjects were measured by enzyme-linked immunosorbent assay (ELISA). The ELISA tests for IL-13 and IL-8 levels were performed using the ELISA (Labsystem, Multi Skan EX, Finland) reader.

Statistical Analysis

When analyzing the data, the nonparametric Kruskal-Wallis H test was used for comparisons between multiple groups. This test only shows whether there is a difference between the groups. For this reason, there is no appropriate post-hoc test. Therefore, post-hoc pairwise comparisons were performed using the Mann-Whitney U test. Statistical analyses were performed using SPSS 14.0, with the Kruskal-Wallis H test used for comparing multiple groups, and the Mann-Whitney U test for post-hoc pairwise comparisons. A p value <0.05 was considered statistically significant.

Results

Group 1 included 30 women and 12 men with symptomatic allergic rhinitis who were not receiving SIT. Their age range was 21-45 years and the disease duration was 5-22 months. Group 2 included 28 women and 14 men with allergic rhinitis who were receiving SIT. They were 23-41 years of age, the disease duration was 8-23 months, and SIT duration was 40-52 months. The control group included 23 healthy individuals (13 female and 10 male) with an age range of 24-40 years (Table 1).

Table 1: Demographic characteristics of the allergic rhinitis patient and control groups

	No SIT (n=42)	SIT (n=42)	Controls (n=23)
Sex (n female/male)	30/12	28/14	13/10
Age (years)	32.5 ± 6.4	34 ± 4.6	31.7 ± 4.69
Disease duration (months)	11.64 ± 4.74	15.81 ± 4.01	-
SIT duration (months)	-	47.48 ± 2.39	-

SIT: Specific immunotherapy

In Group 1, it was determined that 17 patients were allergic to grasses, 7 to tree pollen, and 18 to house dust. The distribution of these allergy types was very similar in Group 2 (18 grass, 6 tree pollen, and 18 house dust allergies) (Table 2). Two-thirds of patients receiving SIT reported no symptoms of allergic rhinitis, while the remaining third had mild symptoms. All patients not receiving SIT had moderate to severe symptoms (Table 2).

Table 2: Clinical characteristics of the allergic rhinitis patient groups

Allergy Type	No SIT n (%)	SIT n (%)
Grass	17 (40.5)	18 (42.9)
Tree pollen	7 (16.7)	6 (14.3)
House Dust	18 (42.9)	18 (42.9)
Symptom Severity		
None	-	28 (66.7)
Mild	-	14 (33.3)
Moderate	21 (50)	-
Severe	21 (50)	-

SIT: Specific immunotherapy

The mean serum IL-13 level was 0.99±0.20 pg/dL in Group 1, 0.72±0.04 pg/dL in Group 2, and 0.57±0.15 pg/dL in the control group. Mean serum IL-8 levels in these groups were 1.07±0.12 pg/dL, 0.77±0.07 pg/dL, and 0.72±0.06 pg/dL, respectively. Statistical comparisons of serum IL-8 and IL-13 between the groups showed that levels of both cytokines were significantly higher in allergic rhinitis patients without SIT than in those with SIT and healthy controls (Table 3) (Figure 1).

Table 3: Comparison of cytokine levels in the allergic rhinitis patient and control groups

	No SIT1 (n=42)	SIT2 (n=42)	Controls3 (n=23)	p value
IL-13 (pg/dL), mean ± SD	0.99 ± 0.20	0.72 ± 0.04	0.57 ±0.15	<0.001, 1 vs. 2,3; <0.001, 2 vs. 3
IL-8 (pg/dL), mean ± SD	1.07 ±0.12	0.77 ±0.07	0.72 ± 0.06	<0.001, 1 vs. 2, 3; 0.004, 2 vs. 3

SIT: Specific immunotherapy

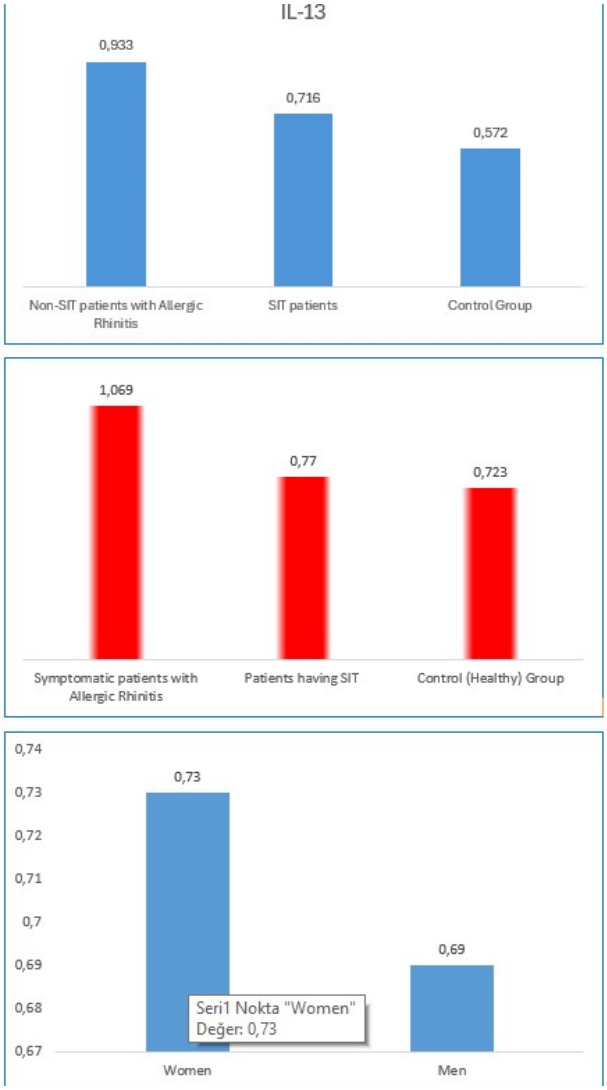

Figure 1

When the serum IL-13 and IL-8 levels were compared between men and women in the groups, no statistically significant differences were observed in Group 1 ($p>0.05$). In Group 2, IL-13 levels were significantly higher among women than men (0.73±0.04 pg/mL vs. 0.69±0.04 pg/mL; $p<0.009$) (Table 4) (Figure 1).

Table 4: Statistical comparison of serum IL-13 and IL-8 levels between males and females in the allergic rhinitis patient groups (Mann-Whitney U test)

	No SIT			SIT		
	Male (n=12)	Female (n=30)	p value	Male (n=14)	Female (n=28)	p value
IL-13 (pg/dL), mean ± SD	0.94 ± 0A5	1.01 ± 0.22	0.238	0.69 ± 0.04	0.73 ± 0.04	0.009
IL-8 (pg/dL), mean ± SD	1.02 ± 0.08	1.08 ± 0.13	0.058	0.76 ± 0.07	0.78 ± 0.07	0.486

SIT: Specific immunotherapy

Discussion

This study included 42 allergic rhinitis patients who were not receiving SIT and were symptomatic, 42 allergic rhinitis patients who were receiving SIT and were asymptomatic, and 23 healthy control subjects. The effect of both immunotherapy and sex on IL-13 and IL-8 levels was examined. There were statistically significant differences in IL-13 and IL-8 between symptomatic allergic rhinitis patients, those who had received SIT, and the control group. However, the only sex-based difference in cytokine levels was between the IL-13 levels of male and female patients who received SIT.

Pawankar et al. reported high levels of IL-13 in patients with allergic rhinitis. Similarly, in our study IL-13 levels were highest among patients with symptomatic allergic rhinitis.[9] We found that IL-13 levels were low in patients who received SIT, consistent with the study by Plewako et al. However, a study by Gogishvili et al. suggested that IL-13 inhibition did not play a major role in the treatment of allergic events. In our study, we observed that IL-13 levels tended to decrease in patients who received SIT.[10,11]

The molar structure of IL-8 is one of the most potent chemoattractants for neutrophils. At the same time, it stimulates the degranulation of polymorphonuclear lymphocytes and the binding of endothelial cells to CD11 and CD18. During the inflammatory response, IL-8 appears relatively later than other chemoattractants. While LTB4 concentration decreases, newly synthesized IL-8 begins to be secreted and exerts its effect for 24 hours. Among the chemokines, RANTES and IL-8 play important roles in eosinophil chemotaxis. Levels of RANTES and IL-8 in nasal lavage and bronchoalveolar lavage fluids were reported to increase after allergen exposure . Similarly, there was a significant difference in serum IL-8 levels between allergic rhinitis patients with and without SIT in our study.[12,13,14]

Lin Chuang et al. examined changes in IL-8 and TNF-alpha levels after SIT in seasonal and non-seasonal allergic rhinitis and found that levels of TNF-alpha and IL-8 were higher in the rhinitis groups than in healthy controls and decreased significantly in rhinitis patients after SIT.[15] In our study, we detected no significant difference between patients who received SIT and the healthy control group. This may be due to the classification of seasonal allergy.

Klein et al. showed that eosinophils concentrations were increased in tissue biopsy samples after nasal allergen exposure and that the cells expressed IL-8, IL-6, IL-13, IL-10, IL-4, and RANTES mRNA. The presence of cells carrying IL-10 and IL-13 mRNA was detected in tissue samples one week after nasal provocation . This supports our method of detecting the effectiveness of SIT in allergic rhinitis patients as a decrease in IL-13 level.[16]

In a study conducted by Kue-Hsiung et al., immunotherapy was administered to children diagnosed with allergic asthma, and analysis of beta chemokine, alpha chemokine, and IL-8 levels in the blood showed that among mite-sensitized patients, those who responded better to immunotherapy had lower beta chemokine and higher IL-8 levels.[17]

Both Rajakulasingam et al. and Klein et al. reported that levels of IL-8 increased after allergen exposure. Similarly, IL-8 levels in our study were highest among symptomatic allergic rhinitis patients. Our results support those of Lin Chuang et al., who reported that IL-8 levels were higher in patients with allergic rhinitis compared to the control group and lower in those receiving immunotherapy.

Numerous studies have demonstrated the efficacy and safety of SIT. The WHO and EAACI have reported that when given at sufficient concentrations, nasal and sublingual administration is as effective and reliable as injections.[18,19] This was confirmed by a 2000 meta-analysis of 54 clinical studies involving asthma patients.[20] In a study conducted by Reha et al., 56 patients receiving SIT and 51 patients receiving pharmacotherapy were examined for 5 years, and it was observed that 44 patients in the SIT group and 33 patients in the pharmacotherapy group were asymptomatic. SIT is shown to significantly reduce symptoms and prevent the development of new sensitization in allergic patients.[21]

In a study conducted by Pifferi et al., a portion of asthmatic patients were given SIT and compared with the untreated control group, and SIT was associated with a significant decrease in symptoms.[22] Waller et al. also showed that seasonal asthma symptoms decreased after SIT with meadow pollen extracts.[23] Dockic et al. examined allergic rhinitis patients receiving immunotherapy for 2 years and observed significant differences in nasal symptoms and skin prick test results between the placebo and study group.[24] Similarly, in the clinical evaluation of the patients in our study, allergic symptoms were nonexistent or mild in patients receiving SIT but ranged from moderate to severe in those not receiving SIT.

Studies in the literature evaluating the relationship between allergic rhinitis and gender reported that the prevalence of allergic rhinitis is higher in women. A retrospective study by Barlay et al. examining 3750 patients in our country also indicated that allergic rhinitis and rhinitis symptoms were more common in women. However, other studies in the literature reported that the frequency of allergic rhinitis is higher in men.[25]

In the present study, we observed no significant sex difference in IL-13 and IL-8 levels among patients not receiving immunotherapy, which supports the literature. Among the patients receiving immunotherapy, the IL-13 level was lower among male patients, while IL-8 levels were similar in male and female patients. Although the involvement of IL-13 and IL-8 in allergic rhinitis has been demonstrated, prospective randomized controlled studies with larger patient series are needed to elucidate the cause of these controversial conflicting results between the sexes. Recent studies have also indicated that immunotherapy not only reduces IL-13 and IL-8 levels but may also play a significant role in altering the Th1/Th2 balance, thereby enhancing the long-term management of allergic rhinitis.[26] This emphasizes the potential of SIT as an effective therapeutic option, further substantiating the findings of our study.

Immunotherapy has proven efficacy in preventing allergic events. Although the exact mechanism of action is not known, changes in cytokine levels are believed to play an important role. Cytokines have a major role in the physiopathology of allergic rhinitis. Of these, eosinophil cationic protein, IL-5, tryptase, IL-4, IL-13, and IL-8 are several important mediators. In our study, IL-8 and IL-13 levels were measured in patients with symptomatic allergic rhinitis, in a group of patients receiving SIT, and in a healthy control group. IL-13 and IL-8 levels were lower in patients receiving immunotherapy, supporting the literature data discussed above. IL-8 and IL-13 are two important mediators involved in allergic rhinitis, and their suppression is one of the mechanisms of action of immunotherapy. However, further studies are needed to investigate the specific roles of IL-13 and IL-8 inhibition in treatment.

Conclusion

The results of this study show that serum IL-13 and IL-8 levels in patients with allergic rhinitis tended to decrease significantly after immunotherapy. When compared according to sex, only IL-13 level differed significantly between men and women receiving immunotherapy.

References

1. Bauchau V, Durham SR. Epidemiological characterization of the intermittent and persistent types of allergic rhinitis. Allergy. 2005;60:350.
2. Bozkurt B, Karakaya G, Kalyoncu AF. Seasonal rhinitis, clinical characteristîcs and risk factors for asthma. Int Arch Allergy Immunol. 2005;138:73-79.
3. Cecil Textbook of Medicine Cilt 2 2006 s(1605-1610).
4. İliçin, Biberoğlu, Süleymanlar, Ünal İç Hastalıkları 2003 Cilt 2 s(2586-2592)
5. Karakaya G. Rinit Epidemiyolojisi. Türkiye Klinikleri J-Allergy-Astma 2002 4:(14-18)
6. Allergy Cytokines in Allergic Inflammation Larry Borish and Lanny J.Rosenwasser Chapter 10 s(108-123)
7. Grammer LC, Greenberger PA. Allergic rhinitis, Patterson's Allergic Disease'(Grammer LC)'den. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2002 s. 159-182
8. Skoner DP. Allergic rhinitis:Defînition,epidemology,patophysology, detection and diagnosis. J Allergy Clin Immunol.2001:108:s2-8
9. Pawankar RU, Okuda M, Hasegawa S,Suzuki K, Yssel H, Okubo K,et al. IL-13 expression in the nasal mucosa of perennial allergic rhinitis. Am J Respir Crit CareMed 1995;152:2059-67
10. Tea Gogishvilli, Christian Hahni Julia Meinhard et al. înhibition of IL-4/IL-13 does not enhance the efficacy of allergen immunoterapy in murin allergic airway inflammation Int Arch Allergy Immunol 2007;142:165-174
11. Halina Plewako, Katarzyna Wosinska, Monica Arvidsson et al. Basophil IL-4 and IL-13 production is supressed during the early phase of rush immunoterapy Int Arch Allergy Immunol 2006;141:346-353
12. Rajakulasingam K,Hamid Q,0'Brien F, Shotman E, Jose PJ, Williams TJ, Et al. RANTES in human allergen induced rhinitis:cellular source and relation to tissue eosinophilia. Am J Respir Crit Care Med 1997;155:696-703
13. Tworek D, Bochehska-Marciniak M, Kupczyk M, Görski P, Kuna P. The effect of 4 weeks treatment with desloratadine (5mg daily) on levels of interleukin (IL)-4, IL-10, IL-18 and TGF beta in patients suffering from seasonal allergic rhinitis Pulm Pharmacol Ther. 2007;20(3):244-9. Epub 2006 Mar 10
14. Dougles JA, Dhami D, Gurr CE, Bulpitt M, Shute JK, Howarth PH, Et al Influence of IL-8 challenge in the nasal mucosa in atopic and non atopic subjects. Am J Respir Crit Care Med 1994,150:1108-13
15. Lin Chuang Er Bi Yan Hou Ke Za Zhi The effect ofTNF alpha and IL-8 in the pathogenesis of allergic rhinitis.2006 Dec;20(23): 1060-1
16. KleinJan A, Dijkstra MD, Boks SS, Severijnen LA, Mulder PG, Fokkens WJ Increase in IL-8, IL-10, IL-13, and RANTES mRNA levels (in situ hybridization) in the nasal mucosa after nasal allergen provocation J Allergy Clin Immunol. 1999 Mar; 103(3 Pt l):441-50.
17. KueHsiung Hsieh,MD,Chen C. Chou,MD, Immnoterapy supressed the production of monocyte chemotactic anda activating factor and augments the production of IL-8 in children asthma 1995 Dec.15Tahami RV, Çorakçıoğlu S,Sonkaya G:Flutikazon Propionatın Perennial Alleıjik Rinitli Hastalarda Klinik Etkinliği, ekimler Yaym Birliği KBB, 1995:1:27-31
18. EAACI. Immunoterapy.Position paper. Allergy. 1988;43:1-33
19. Bousquet j,Lockey R,Mailing HJ.A Allergen Immunoterapy:therapeutic vaccines for allergic diseases. A WHO position paper.. J Allergy Clin Immunol.l 998; 102(4 Pt l):558-62
20. Abramson MJ., Puy RM,Weiner JM. Allergen Immunoterapy for asthma. Cochrane database Syst Rev 2003;(4):CD001186
21. CM Reha, A Ebru. Specific immunoterapy is effective in the prevention of new sensitivities. Allergologia et immunopatologia. March 2007. Volume 35- number 02 p.44-51
22. Pifferi M, Baidini G, Marazzını G et al. Benefîts of immunoterapy with a standardized Dermatophagoides pteronyssinus extract in asthmatic children: a three year prospective study. Allergy.2002;57:785-90
23. Walker SM. Grass pollen immunoterapy for seasonal rhinitis and asthma: a randomized, controlled trıal. J Allergy Immunol. 2001;107:87-93
24. Dockid D,Schnitker J,Narkus A. Clinical effects of spesıfic immunoterapy: A two year double-blind, placebo-controlled study with a one year follow up. Clinic of Pulmonology and AUergology,2005 Dec; 26(2):113-2
25. Dr. Fevzi Barlay Prof. Dr. Bülent Topuz Denizli ili ve çevresindeki alerjik rinit ön tanılı olgularda deri prick testi sonuçlarımız; 15 yıllık retrospektif çalışma uzmanlık tezi Denizli – 2019
26. Wang, J., Zhou, Y., Zhang, H. et al. Pathogenesis of allergic diseases and implications for therapeutic interventions. Sig Transduct Target Ther 2023;8(138).