Original Article

Impact of Immunotherapy on Refractory Allergic Rhinitis in Armed Force Hospital Southern Region, Saudi Arabia

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Abstract

Background: One of the most common types of allergies is allergic rhinitis (AR). According to recent studies, its prevalence has fluctuated from 1.4% to 45% in the last few decades. AR has both direct and indirect consequences on one's quality of life, and it's often accompanied by asthma, middle ear irritation, nasal polyps, sinusitis, and lower respiratory tract infections. There is evidence that AR is frequently undertreated, mainly in its moderate and severe/intense persistent forms. The management of patients with AR involves proper pharmacological therapies, including allergen immunotherapy. Immunotherapy with allergens has been shown to be effective in the treatment of AR, asthma, and insect sting allergies. **Objectives:** The objective of this study was to measure the impact of immunotherapy on refractory AR patients in armed force hospital southern region, Saudi Arabia. In addition to detect the minimal duration required for immunotherapy. **Materials and Methods:** The study was conducted as an quasi-experimental intuitional – based study, total number of 52 patients used in this study which is all patients who fulfilled the inclusion criteria and initiated immunotherapy for refractory AR during period from Jan 2019 to Oct 2021, Data was collected using standardized online self-administered questionnaires using google forms. **Results:** A total of 52 patients responded to the questionnaire. About two-thirds of patients were males (67.3%), and aged 21–40 years (76.9%). The majority of them had a history of chronic rhinosinusitis (90.4%), whereas less than half of the patients had bronchial asthma (46.2%), nasal polyps (36.5%) and skin allergy (36.5%). Regarding the characteristics of immunotherapy, about one-quarter of the patients were receiving the immunotherapy for less than 6 months (26.9%), whereas 32.7%, 36.5% and 3.8% of them were receiving the therapy for 7 months to 1 year, more than 1 year to 2 years and more than 2 years, respectively. The reliability of the SNOT-22 scale was excellent as indicated by a Cronbach's alpha (α = 0.907). The most common problematic aspects before the immunotherapy (responses ranging from moderate to bad problems) were related to sneezing (96.1%), blockage/congestion of nose (94.2%) and runny nose (92.3%). These problematic aspects were indicated by 17.3%, 15.3% and 11.5% of patients after the intervention, respectively. The overall SNOT-22 score decreased significantly after the immunotherapy compared to before the intervention (median = 79.5, interquartile range [IQR] = 67.5–87.0 before the intervention and median = 18.0, IQR = 13.5–23.0 after the intervention, $P < 0.0001$). Similarly, the median values of all items of the SNOT-22 questionnaire reduced significantly ($P < 0.0001$ for all). The percentage improvement of the SNOT-22 score was 71.3% ±19.5 for the whole sample. Results of the correlation testing revealed a significant association between the pre-immunotherapy score and the percentage improvement (Spearman correlation coefficient = 0.32, $P = 0.019$), which indicates that patients with higher pre-therapeutic scores had a greater improvement with immunotherapy. Considering the factors associated with percentage improvement, results showed that the improvement in the overall SNOT-22 score differed significantly based on the duration of immunotherapy. **Conclusion:** As overall, this study can conclude that sublingual immunotherapy as treatment of AR led to a reduction in all symptoms studied, improving the quality of life of patients, proving itself as an important therapeutic tool for these pathological conditions. In addition to that, it has a known and relatively low risk of severe adverse events. Furthermore, a significant association was noted between the preimmunotherapy score and the percentage improvement which indicates that patients with higher pretherapeutic scores had a greater improvement with immunotherapy.

Keywords: *Allergen immunotherapy, allergic rhinitis, Saudi Arabia, sublingual immunotherapy*

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Introduction

One of the most common types of allergies is allergic rhinitis (AR). According to recent studies, its prevalence has fluctuated from

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1.4% to 45% in the last few decades. AR has both direct and indirect consequences on one's quality of life, and it's often accompanied by asthma, middle ear irritation, nasal polyps, sinusitis, and lower respiratory tract infections.[1]

AR is a global health problem and its prevalence has increased considerably in the last two decades. Treatment includes allergen avoidance, drugs such as antihistamine tablets and nasal sprays, and immunotherapy (vaccination). For those patients whose symptoms remain uncontrolled despite drug treatment, specific immunotherapy (SIT) allergen is advised.[2]

When there are no signs of lower respiratory tract infections or anatomic abnormalities of the nose, AR is diagnosed solely on clinical symptoms such as sneezing, rhinorrhea, itchy nose, and nasal congestion. When lab evidence, such as a positive prick test and immunoglobulin E (IgE) specific antibody, plus the patient's history and physical examination, are in favor of allergy.[3]

There is evidence that AR is frequently undertreated, mainly in its moderate and severe/intense persistent forms. The management of patients with AR involves proper pharmacological therapies, including allergen immunotherapy.[4]

AR treatment may involve appropriate environmental control measures aimed at lowering allergen load,[5] medication and allergy immunotherapy (AIT). Only AIT establishes immunologic tolerance to the specific allergens that cause allergy symptoms among these treatments.[6]

Immunotherapy with allergens has been shown to be effective in the treatment of AR, asthma, and insect sting allergies.[1]

AIT is approved as a treatment option for patients with AR and/or asthma who have symptoms that are not responding to pharmacotherapy and who have troublesome pharmaceutical side effects, according to US and international recommendations.

Patients who are hesitant to use drugs continuously to control or "mask" rather than cure their allergic disease are said to have a patient preference.[7]

In the United States, there are two types of AIT that have been approved by the Food and Drug Administration: subcutaneous immunotherapy (SCIT) and sublingual immunotherapy (SLIT). Each method has its own set of benefits and drawbacks.[8]

Although SCIT is a well-established effective treatment for seasonal and perennial allergic diseases,[9] it has the drawback of requiring administration in a physician's office or clinic with appropriate emergency equipment and personnel trained to recognize and manage serious allergic reactions such as anaphylaxis. SLIT has evolved as a new type of successful AIT that has the benefit of being less time consuming.[10]

Subcutaneous injection with allergen-SIT is indicated for patients with refractory symptoms, being considered the only treatment capable of modifying the course of AR and asthmas. However, <5% of allergic patients have undergone immunotherapy, mainly due to the long term for treatment and allergy side effects, which demonstrates the complexity of this therapy. Moreover, different authors show that the actual beneficial effects and security of immunotherapy remain unclear.[4]

Problem statement

AR is the most common of the allergic diseases. Despite improved understanding of the pathophysiology of AR and advances in its pharmacological treatment, its prevalence has increased worldwide. For patients whose symptoms remain uncontrolled despite medical treatment, allergen injection immunotherapy is advised. An allergen-based treatment may reduce symptoms, the need for medication and modify the natural course of this disease.

Justification

AR is one of the most common allergic diseases and characterized by sneezing, rhinorrhea, nasal congestion and nasopharyngeal itching. SLIT for specific allergens is an effective treatment and induces the inhibitory effect of T regulatory lymphocytes and decreases clinical symptoms in AR.

Study objective

The objective of this study was to measure the impact of immunotherapy on refractory AR patients in armed force hospital southern region, Saudi Arabia. In addition to detect the minimal duration required for immunotherapy.

Hypothesis

SLIT improves symptom and/or medication scores and validated quality of life measures. In addition, SCIT is safe when administered to carefully selected patients and in settings capable of responding to systemic reactions.

Materials and Methods

Study design

The study was conducted as an quasi-experimental intuitional–based study.

Study area

The study was conducted in Armed Force Hospital Southern Region, Kingdom of Saudi Arabia. Which is tertiary hospital with bed capacity more than 600.

Study population

All Patients who started immunotherapy in armed force hospital southern region during the period from January 2019 to October 2021.

Inclusive criteria

Any patient (male or female-any age) with refractory v attended Armed Force Hospital Southern Region during the period from January 2019 to October 2021 who started immunotherapy in Aseer region, and who accepted to participate in this study.

Refractory AR defined as: Inflammatory, IgE mediated disease characterized by nasal congestion, rhinorrhea, sneezing and nasal itching that is not controlled or poorly controlled with maximum medical therapy (e.g.: Avoidance measures, INCS, antihistamine, leukotriene receptor antagonist).

Exclusive criteria

- Patients with AR who improved by traditional management
- Patients not in Aseer region
- Patients who failed to complete the questionnaire
- Patients who refused to participate in this study.

Period of study

November 2021 to April 2022.

Sample size

Total number of 52 patients used in this study which is All patients who fulfilled the inclusion criteria and initiated immunotherapy for refractory AR during the period (January 2019 to October 2021) were invited to participate in the study.

Data collection

Data was collected using standardized online self-administered questionnaires using Google forms.

Data collection tools

A structured and self-administrated electronic questionnaire was used in the study for data collection. It was a questionnaire created on the basis of intensive literature by researchers. Examination and consultancy of experts were done to meet the requirements of the ideal questionnaire. The questionnaire from the report was open for 3 months till no more new responses were achieved. The questionnaire included the following data:

1. Demographic
2. Past medical history and comorbidity
3. Family history
4. Comparison base on SNOT-22 questionnaire between pre- and post immunotherapy and so on.

The final approved questionnaire was uploaded online using social media platforms by the researchers and their friends.

Plan for data analysis

Data collected was computerized through Microsoft Excel. The data was analyzed through SPSS (Statistical package for the social sciences) Version 21. The data was presented graphically (frequency tables, graphs). Median with interquartile range was used to display quantitative variables which don't follow normal distribution while test of significance assessed any significant relations.

Ethical consideration

It was sought from the research technical and ethical committee at the Faculty of Medicine. An informed ethical consent has been taken from the participants. No personal data or information were included in the questionnaire to ensure the participants' privacy and confidentiality.

Results

Demographic and clinical characteristics

A total of 52 patients responded to the questionnaire. About two-thirds of patients were males (67.3%), and aged 21–40 years (76.9%). The majority of them had a history of chronic rhinosinusitis (90.4%), whereas less than half of the patients had bronchial asthma (46.2%), nasal polyps (36.5%) and skin allergy (36.5%). Regarding the characteristics of immunotherapy, about one-quarter of the patients were receiving the immunotherapy for less than 6 months (26.9%), whereas 32.7%, 36.5% and 3.8% of them were receiving the therapy for 7 months to 1 year, more than 1 year to 2 years and more than 2 years, respectively [Table 1].

Familial and personal characteristics of allergy

In general, 61.5% of the patients had a positive family history of an allergic condition. Interestingly, all the patients underwent a skin allergy test, and none of them underwent a lab blood test. Allergy test results showed a total of 95 allergens among the patients under study. The most common allergens were two species of pollens, including the pollens of bermuda grass (27.4%) and rye grass (17.9%) as well as two species of mites, including *Dermatophagoides pteronyssinus* (10.5%) and *Dermatophagoides farinaa* [9.5%, Figure 1a]. The most frequently self-reported triggers of allergy included the perfume (34.7%), soap powder (20.4%) and air conditions [18.4%, Figure 1b].

Characteristics of the SNOT-22 scale

The reliability of the SNOT-22 scale was excellent as indicated by a Cronbach's alpha ($\alpha = 0.907$). The detailed responses of patients to the SNOT-22 scale are depicted in Figure 2. The most common problematic aspects before the immunotherapy (responses ranging from moderate to bad problems) were related to sneezing (96.1%), blockage/congestion of nose (94.2%) and runny nose [92.3%, Figure 2a]. These problematic aspects were indicated by 17.3%, 15.3% and 11.5% of patients after the intervention, respectively [Figure 2b].

Table 1: Demographic and clinical characteristics

Parameter	Category	Frequency (%)
Gender	Male	35 (67.3)
	Female	17 (32.7)
Occupation	Student	13 (25)
	Employed - Private	4 (7.7)
	Employed - Government	10 (19.2)
	Military	8 (15.4)
	Not working	7 (13.5)
	Self-employed	3 (5.8)
	Other	7 (13.5)
Place of residence	Khamis Mushait	22 (42.3)
	Ahad Rafidah	4 (7.7)
	Jazan	5 (9.6)
	Muhayil	3 (5.8)
	Abha	9 (17.3)
	Najran	1 (1.9)
	Al Wadeen	3 (5.8)
	Others	5 (9.6)
Age (years)	Below 20	7 (13.5)
	21–30	19 (36.5)
	31–40	21 (40.4)
	41–50	4 (7.7)
	51 and above	1 (1.9)
Clinical history		
Bronchial asthma	Yes	24 (46.2)
Chronic rhinosinusitis	Yes	47 (90.4)
Nasal polyps	Yes	19 (36.5)
Skin allergy	Yes	19 (36.5)
High blood pressure	Yes	0
Diabetes mellitus	Yes	2 (3.8)
Current smoking	Yes	15 (28.8)
A history of COVID	Yes	19 (36.5)
Duration of immunotherapy	<6 months	14 (26.9)
	7 months to 1 year	17 (32.7)
	>1 year to 2 years	19 (36.5)
	>2 years	2 (3.8)

Characteristics of and changes in the SNOT-22 score

The overall SNOT-22 score decreased significantly after the immunotherapy compared to before the intervention [median = 79.5, interquartile range (IQR) = 67.5–87.0 before the intervention and median = 18.0, IQR = 13.5-23.0 after the intervention, $P < 0.0001$, Figure 3]. Similarly, the median values of all items of the SNOT-22 questionnaire reduced significantly [$P < 0.0001$ for all, Table 2].

The percentage improvement of the SNOT-22 score was 71.3% ±19.5 for the whole sample. Results of the correlation testing revealed a significant association between the preimmunotherapy score and the percentage improvement (Spearman correlation coefficient = 0.32, $P = 0.019$), which indicates that patients with higher pretherapeutic scores had a greater improvement with immunotherapy [Figure 4].

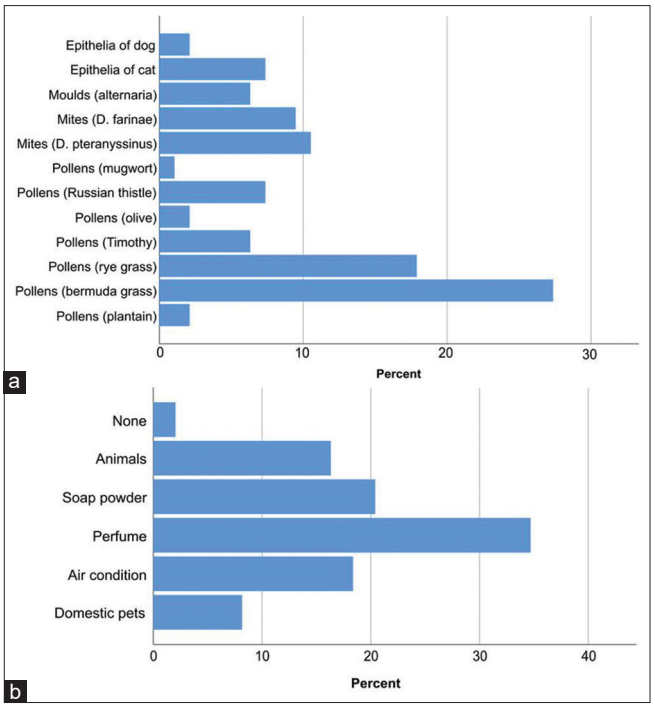

Figure 1: The percentage distribution of allergic test results

Factors associated with SNOT-22 improvement

Considering the factors associated with percentage improvement, results showed that the improvement in the overall SNOT-22 score differed significantly based on the duration of immunotherapy [Table 3]. Results of pairwise comparisons showed that patients who received an immunotherapy for >1–2 years had significantly higher SNOT-22 scores than those receiving the therapy for <6 months [adjusted difference = 16.4, standard error = 5.3, $P = 0.013$, Table 4].

Discussion

The main object of the study was to measure the impact of immunotherapy on refractory AR patients in armed force hospital southern region, Saudi Arabia. In addition to detecting the minimal duration required for immunotherapy.

The questionnaire was completed by 52 patients. About two-thirds of the patients (67.3%) were men between the ages of 21 and 40 (76.9%). The bulk of them (90.4%) had chronic rhinosinusitis, while bronchial asthma (46.2%), nasal polyps (36.5%), and skin allergies were found in less than half of the patients (36.5%). All of these findings corroborate those reported in prior studies on the same subject.

The sample size in our study is average when compared to other previously done studies found in LR, one study was done among 25[11] participants and another study was done including 191 participants.[12] The findings of allergy

Table 2: Characteristics of and changes in the Sino-nasal outcome test-22(SNOT-22) scores

Parameter	Preimmunotherapy	Postimmunotherapy	*Z**	*P**
Need to blow nose	3.0 (2.0–4.0)	1.0 (0.0–1.0)	−6.15	<0.0001
Sneezing	4.0 (4.0–5.0)	1.5 (1.0–2.0)	−6.05	<0.0001
Runny nose	4.5 (4.0–5.0)	1.0 (1.0–2.0)	−5.84	<0.0001
Blockage/congestion of nose	5.0 (4.0–5.0)	1.0 (1.0–2.0)	−5.96	<0.0001
Sense of taste/smell	3.5 (2.5–4.0)	0.0 (0.0–1.0)	−5.78	<0.0001
Cough	2.0 (1.0–4.0)	0.0 (0.0–1.0)	−5.49	<0.0001
Post nasal discharge	3.5 (3.0–4.0)	1.0 (0.0–1.0)	−6.00	<0.0001
Thick nasal discharge	4.0 (3.0–4.0)	1.0 (0.0–1.0)	−6.09	<0.0001
Ear fulness	2.5 (1.0–4.0)	0.0 (0.0–0.5)	−5.56	<0.0001
Dizziness	3.0 (1.5–4.0)	0.5 (0.0–1.0)	−5.38	<0.0001
Ear pain/pressure	2.0 (0.0–3.0)	0.0 (0.0–0.0)	−5.21	<0.0001
Facial pain/pressure	3.5 (2.5–4.0)	0.5 (0.0–1.0)	−5.84	<0.0001
Difficulty falling asleep	4.0 (4.0–5.0)	1.0 (0.0–2.0)	−6.15	<0.0001
Waking up at night	3.5 (2.0–4.0)	0.0 (0.0–1.0)	−6.08	<0.0001
Lack of a good night sleep	5.0 (4.0–5.0)	1.0 (0.0–1.0)	−5.89	<0.0001
Waking up tired	5.0 (4.0–5.0)	1.0 (1.0–2.0)	−5.96	<0.0001
Fatigue during the day	4.5 (3.0–5.0)	1.0 (1.0–2.0)	−5.88	<0.0001
Reduced productivity	4.0 (3.0–4.0)	1.0 (0.0–1.0)	−5.93	<0.0001
Reduced concentration	4.0 (3.5–5.0)	1.0 (0.0–1.0)	−5.94	<0.0001
Frustrated/restless/irritable	5.0 (4.0–5.0)	1.0 (0.0–1.0)	−5.93	<0.0001
Sad	4.0 (2.0–4.0)	0.0 (0.0–1.0)	−5.52	<0.0001
Embarrassed	3.0 (1.5–4.0)	0.0 (0.0–1.0)	−5.50	<0.0001
Total SNOT-22 score	79.5 (67.5–87.0)	18.0 (13.5–23.0)	−6.28	<0.0001

Z values and *P* values of Wilcoxon signed ranks test. Results are expressed as medians and IQRs. IQRs: Interquartile ranges, SNOT: Sino-nasal outcome test

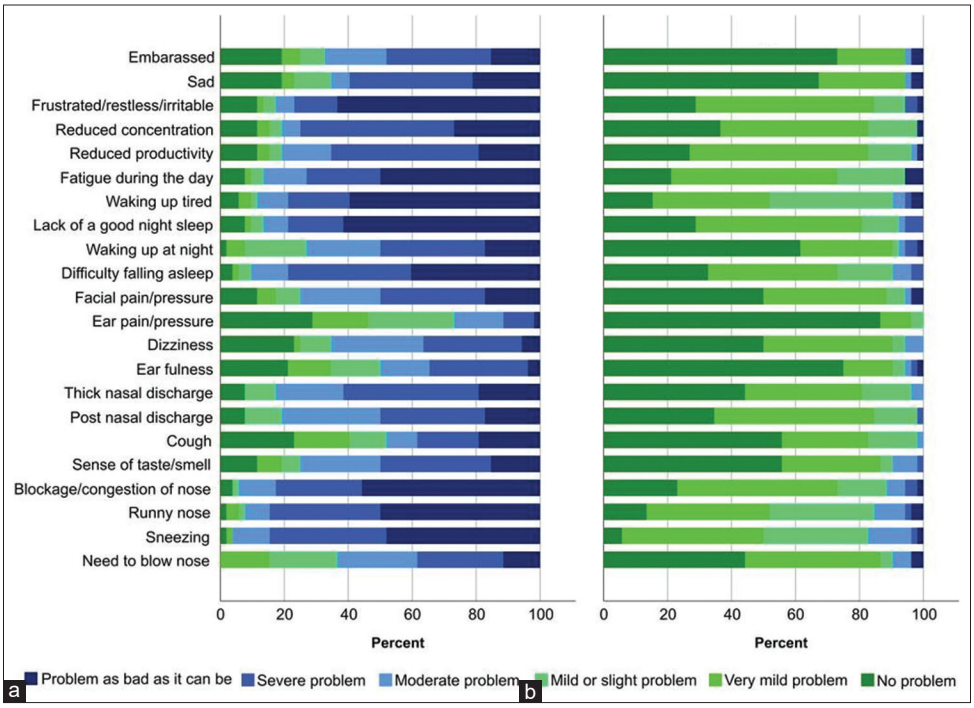

Figure 2: Patients responses to the SNOT-22 questionnaire before (a) and after (b) the immunotherapy. SNOT: Sino-nasal outcome test

tests revealed that the patients under research were allergic to a total of 95 allergens. Two pollen types, bermuda grass (27.4%) and rye grass (17.9%), as well as two mite species, *D. pteranyssinus* (10.5%) and D. farinaa (10.5%), were the most prevalent allergens [9.5%, Figure 1a], in our study we didn't specify the treatment and study population

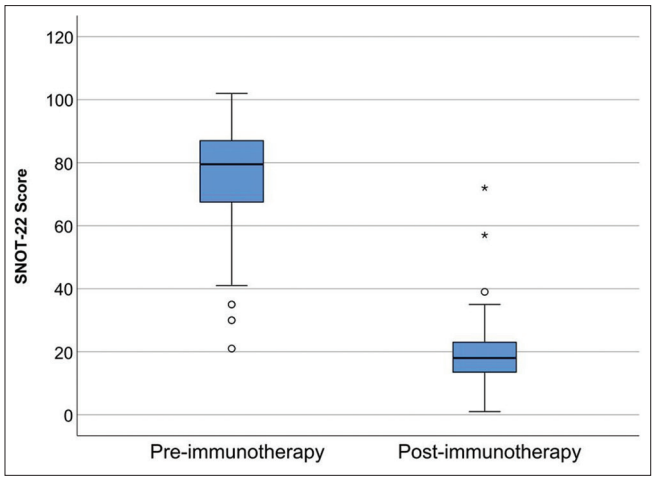

Figure 3: A box plot showing the median values of SNOT-22 scores before and after the immunotherapy. SNOT: Sino-nasal outcome test

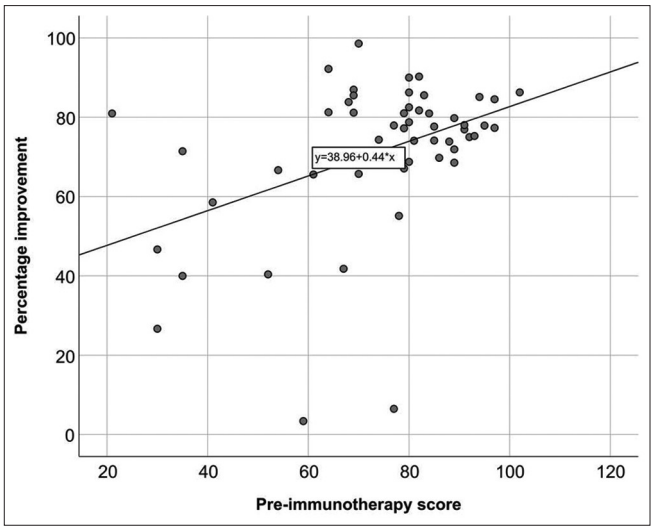

Figure 4: A scatterplot depicting the correlation between the SNOT-22 score before the immunotherapy and the percentage improvement in the SNOT-22 score. SNOT: Sino-nasal outcome test

Table 3: Factors associated with changes in the SNOT-22 score

Parameter	Category	Percentage improvement in SNOT-22 score	*P*
Gender	Male	77.3 (71.4–82.5)	0.344
	Female	73.9 (58.5–79.8)	
Age (years)	Below 20	75.3 (68.8–81.0)	0.254
	21–30	78.0 (74.3–85.5)	
	31–40	76.9 (65.7–84.5)	
	41–50	69.9 (53.0–77.7)	
	51 and above	3.4 (3.4–3.4)	
Duration of immunotherapy	<6 months	50.9 (40.0–77.2)	0.015
	7 months to 1 year	77.7 (71.9–81.3)	
	>1 year to 2 years	79.8 (75.0–84.5)	
	>2 years	77.9 (68.8–87.0)	

Results are expressed as medians and IQRs. IQRs: Interquartile ranges, SNOT: Sino-nasal outcome test

Table 4: Pairwise comparisons of different categories of the duration of immunotherapy and the percentage improvement in SNOT-22 scores

Sample 1-Sample 2	Test statistic (SE)	*P**
<6 months-7 months to 1 year	−13.3 (5.5)	0.088
<6 months->2 years	−16.0 (11.5)	0.981
<6 months->1 year to 2 years	−16.4 (5.3)	0.013
7 months to 1 year->2 years	−2.6 (11.3)	0.999
7 months to 1 year->1 year to 2 years	−3.0 (5.1)	0.999
>2 years-> 1 year to 2 years	0.4 (11.3)	0.999

**P* values are adjusted the Bonferroni correction for multiple tests. SE: Standard error, SNOT: Sino-nasal outcome test

according to type of allergen as previous study conducted in Bulgaria and published in 2017.[12]

The SNOT-22 questionnaire that was used in our study was in Arabic version and it was validated, while some previous studies used rhinoconjuctivitis quality of life questionnaire,[11] and another study didn't specify the AR questionnaire used.[12]

When compared to before the intervention, the overall SNOT-22 score reduced significantly [median = 79.5, IQR = 67.5–87.0 before the intervention and median = 18.0, IQR = 13.5–23.0 after the intervention, $P = 0.0001$, Figure 3]. Similarly, all of the SNOT-22 questionnaire's median scores decreased dramatically [$P = 0.0001$ for all, Table 2]. These finding found in our study agree with all previously done studies on the same topic.

Sneezing (96.1%), blockage/congestion of the nose (94.2%), and runny nose (92.3%) were the most prevalent issues prior to immunotherapy (responses ranging from moderate to severe difficulties). After the intervention, 17.3%, 15.3%, and 11.5% of patients acknowledged these troublesome features, respectively. All of these previous symptoms come under the umbrella of nasal symptoms, and when compared to previous studies which show the greatest difference before and after SLIT, it was observed in the nasal symptoms followed by practical symptoms, and activities for patient treated with house dust mite and also greatest determined in eye symptoms, followed by nasal symptoms and practical symptoms in patients treated with grass pollen extract.[12]

The correlation testing demonstrated a significant relationship between preimmunotherapy score and percentage improvement (Spearman correlation coefficient = 0.32, $P = 0.019$), implying that patients with higher pretherapeutic scores improved more with immunotherapy, and this finding was not mentioned in any of the previously done studies on the same topic.

The improvement in the overall SNOT-22 score changed significantly depending on the length of immunotherapy,

according to the findings [Table 3]. Patients who received immunotherapy for more than 1 to 2 years had significantly higher SNOT-22 improvement scores than those who had it for <6 months [adjusted difference = 16.4, standard error = 5.3, $P = 0.013$, Table 4]. This finding is consisting with those found in previous study which show that patients treated with grass pollen extract had a better quality of life. In a randomized research, Nelson *et al*. found that Timothy grass SLIT improved QOL after one season of treatment. The authors of another DBPC experiment using grass pollen pills found that this treatment improved QOL with long-term efficacy 2 years after treatment completion.[13]

Our study demonstrates the effectiveness of SLIT for patient with moderate to severe AR for which we need to apply it more in clinical practice, and also detects that SLIT can also be effective after duration less than recommended duration which is 3 years.

The study does have certain drawbacks. There was no control group and the sample size was considered small. Another problem is that concomitant disorders can impair SNOT-22 which causing the results to be affected.

Other limitation in our study was that the questionnaire was not obtained at baseline before starting SLIT.

The main strength of our study is that it is not specific for on type of SLIT, also the SNOT-22 use is disease specific, in addition there was no time limit in our study for duration of treatment which give us idea about the minimum duration required for SLIT to be effective.

Conclusion

As overall, this study can conclude that SLIT as treatment of AR led to a reduction in all symptoms studied, improving the quality of life of patients, proving itself as an important therapeutic tool for these pathological conditions. In addition to that, it has a known and relatively low risk of severe adverse events. Furthermore, a significant association was noted between the preimmunotherapy score and the percentage improvement which indicates that patients with higher pretherapeutic scores had a greater improvement with immunotherapy.

Recommendations

- Immunotherapy should be used more often for patients with AR
- Patients with severe AR should be counseled and advised to take immunotherapy
- Clinical trials should be done more often to assess the risk factors for complications after using immunotherapy for patients with AR
- More studies on this topic should be conducted in Saudi Arabia to strengthen this evidence base for clinical decision making.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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