

Assessment of Effect of Subcutaneous Immunotherapy on the Quality of Life of Allergic Rhinitis Children

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ABSTRACT

Background: When it comes to treating children with respiratory allergies and allergic rhinitis, allergen-specific immunotherapy is a crucial choice.

Objective: This study aimed to assess the impact of immunotherapy (AIT) on quality of life in children with allergic rhinitis.

Subjects and methods: In a randomized-controlled trial we conducted this study at Pediatric Outpatient Clinic at Zagazig University Hospitals on 40 pediatrics with allergic rhinitis, randomly allocated into 2 equal groups: the Immunotherapy group received (AIT + pharmacotherapy) and pharmacotherapy group received pharmacotherapy only.

Results: The quality of life score started to show significant improvement after five weeks of start of immunotherapy for immunotherapy group and this improvement continued till the end of six months therapy, Total Nasal Symptoms (TNS) score started to show significant improvement after six weeks of start of immunotherapy for immunotherapy group and this improvement continued till the end of six months therapy. Significant improvement occurred in quality of life questionnaire score and in Total Nasal symptoms score among the immunotherapy group with a percentage of 77.97% and 81.67% respectively. There was statistically significant relation between percentage of improvement in quality of life questionnaire score and seasonality (Perennial Allergic Rhinitis is associated with better improvement).

Conclusion: Subcutaneous Immunotherapy was safe and effective in the treatment of the Allergic Rhinitis in children. It resulted in significant improvement in QoL and symptoms through the study period, and this improvement was higher than in the pharmacotherapy only group. Subcutaneous immunotherapy was associated with minor adverse events.

Keywords: Subcutaneous immunotherapy, Allergic rhinitis, Quality of Life.

INTRODUCTION

About 20% of the population suffers from allergic rhinitis (AR) with or without conjunctivitis, making it one of the most common allergic disorders⁽¹⁾. Asthma-related AR has negative effects on patients' emotional and physical health, as well as their academic and social functioning as well as quality of life (QoL)⁽²⁾.

Rising rates of childhood AR call for more research on the effect of disease-modifying treatments have on quality of life⁽²⁾. Both educational measures and pharmaceutical therapy are advocated for the treatment of respiratory allergies. These typically result in good symptom control, but they do nothing to address the underlying immunological issue or alter the disease's inevitable progression⁽³⁾.

Allergen avoidance, medication, allergen immunotherapy (AIT), and patient education are recommended as part of the ideal treatment plan for allergic rhinitis in a World Health Organization position paper⁽⁴⁾. When it comes to treating respiratory allergies, allergen-specific immunotherapy is a viable alternative, and it also has a disease-modifying effect that is not shared by pharmaceutical treatments⁽⁵⁾.

Purified extracts of specific allergens are given to patients on a regular basis as part of AIT. This chronic challenge modifies the patient's immunological profile by inducing the release of immunosuppressive cytokines and directing the immune response toward the generation of Th1 and

regulatory T-cell (Treg) lymphocytes⁽⁶⁾.

We aimed to assess the impact of immunotherapy (AIT) on quality of life in children with allergic rhinitis.

PATIENTS AND METHODS

We conducted randomized-controlled study at Pediatric Outpatient Clinic at Zagazig University Hospitals on 40 pediatrics with allergic rhinitis according to **Allergic Rhinitis and its Impact on Asthma (ARIA) Guidelines update**⁽⁷⁾ based on recurrent attacks of typical nasal symptoms (blockage, nasal itching, rhinorrhea and sneezing). That were reversible spontaneously or with medical treatment.

Patients enrolled in the study were classified into 2 groups: Immunotherapy group consisted of 20 allergic rhinitis children. They received subcutaneous allergen immunotherapy (SCIT) in addition to traditional pharmacotherapy.

Pharmacotherapy Group: consists of 20 patients, age and sex matched group of Allergic Rhinitis children, they received pharmacotherapy only.

Inclusion criteria: Age: 5 – 17 years. Sex: both sexes were included.

Allergic Rhinitis children diagnosed clinically with all of the following criteria: (1) Nasal Symptoms

strongly suggestive of AR, with or without conjunctivitis (at least 2 nasal symptoms: rhinorrhea, blockage, sneezing, or itching). (2) Approved allergen sensitivity, correlation between clinical history and evidence of IgE sensitization to one or more clinically relevant aeroallergens (either a positive skin prick test or positive serum-specific IgE). (3) Experience moderate-to-severe symptoms, which interfere with usual daily activities or sleep despite regular and appropriate pharmacotherapy and/or avoidance strategies.

Exclusion criteria: Uncontrolled or severe asthma. Active, systemic autoimmune disorders (unresponsive to treatment). Active malignant neoplasia. Severe systemic illness, chronic comorbidity including skin disease. If the patient has severe reactions to injections on multiple occasions or experiences anaphylaxis once, immunotherapy should be stopped ⁽⁸⁾.

For each case entered in the study:

1. Full Clinical history.
2. Full clinical examination to reveal allergic salute and shiners, local examination of the nose including assessment of symptoms, and examination of the ears, sinuses, and posterior oropharynx.
3. Routine laboratory investigations and serum total IgE: Total serum IgE levels were measured using commercially available kits [Enzyme Linked Immunosorbents Assay (ELISA): (Immunoglobulin E (IgE) ELISA KIT, ab178659)].
4. Skin prick test (SPT): If the patient was allergic to the allergen being tested, a red flare would emerge around a small wheal that would cause the patient discomfort. When testing for specific IgE to an allergen, a wheal that was 3 mm or greater compared favourably to the negative control was declared positive. The patient's medical record was then compared to the findings. The SPT detects the presence of IgE antibodies against specific allergens with a high degree of sensitivity and specificity. Patients were monitored for at least 30 minutes after the test ended so that any adverse effects could be handled.
5. Severity of nasal symptoms assessed before and after initiation of Allergen Immunotherapy (AIT) using total nasal symptom score (TNS): Allergen immunotherapy (AIT) was prescribed for the patients of immunotherapy group in addition to traditional pharmacotherapy according to the results of skin prick test done before. After treatment monitoring for adverse reactions, All patients remained under observation for 30 min after injections. The size of the local weal and flare response and any local swelling around the injection site was recorded: (a) Symptomatic local

swelling = ice pack, oral non-sedating antihistamine were considered. In general, these swellings are to be expected and are well-tolerated. (b) Mild or moderate systemic reaction (e.g., rhinitis, flushing, urticaria) = oral non-sedating antihistamine and observation till resolution of symptoms. (c) Severe systemic reaction, severe symptoms, rapid progression of symptoms, or signs of anaphylaxis were indications for early use of adrenaline. 1:1000 adrenaline IMI (0.01mg/kg to a maximum of 0.5mg) was considered. The total nasal symptoms score (TNS) was the sum of the scores for the individual symptoms. Values (0–12) were categorized as mild (0–4), moderate (5–8), and severe (9–12) ⁽⁹⁾.

6. The quality of life (QoL) assessed before and after initiation of allergen immunotherapy (AIT) using rhinoconjunctivitis quality-of-life questionnaire (RQLQ). We used the disease-Specific quality-of-life questionnaires designed by **Juniper et al.** ⁽¹⁰⁾ and their age specific adaptations; The Adolescent Rhinoconjunctivitis quality of life (ARQLQ) for patients 12 to 17 years of age and, the Pediatric Rhinoconjunctivitis quality of life (PRQLQ) for patients 5 to 12 years of age ⁽¹⁰⁾.
7. Disease severity and quality-of-life were assessed weekly for six months in both groups.

Ethical approval:

The Faculty of Medicine, Zagazig University gave its ethical approval for this investigation. Written consents were obtained from all parents of enrolled subjects in the study. The Helsinki Declaration was upheld throughout the course of the investigation.

Statistical analysis

Statistical Package for the Social Sciences (SPSS) version 20 was used. Quantitative data were typically shown as a mean and SD, while qualitative data were shown as raw numbers or percentages. The significance of differences was examined using the following tests: Chi-square test for comparing frequencies (qualitative variables) and percentages (groups). The t test, the Man Whitney test, the paired t test, and the analysis of variance (ANOVA) can all be used to compare the means of several different quantitatively independent groups. Results were considered significant when the P value ≤ 0.05 and highly significant when it was ≤ 0.001 .

RESULTS

Table (1) showed that there was no statistically significant difference between both groups as regards demographic data (age, sex, or residence).

Table (1): Comparison between the studied groups regarding demographic data

	Immunotherapy group N=20 (%)	Pharmacotherapy group N=20 (%)	χ^2	P
Sex:				
Female	8 (40%)	7 (35%)	0.107	0.744
Male	12 (60%)	13 (65%)		
Residence:				
Rural	11 (55%)	8 (40%)	0.902	0.342
Urban	9 (45%)	12 (60%)		
	Median (IQR)	Median (IQR)	Z	P
Age (year)	8(6.25 – 11)	8(7 – 11)	-0.205	0.838

Z Mann Whitney test, IQR interquartile range, Chi square test

Figure (1) showed that the most common allergens found among study subjects were mixed pollens, Dust mites and Hay Dust.

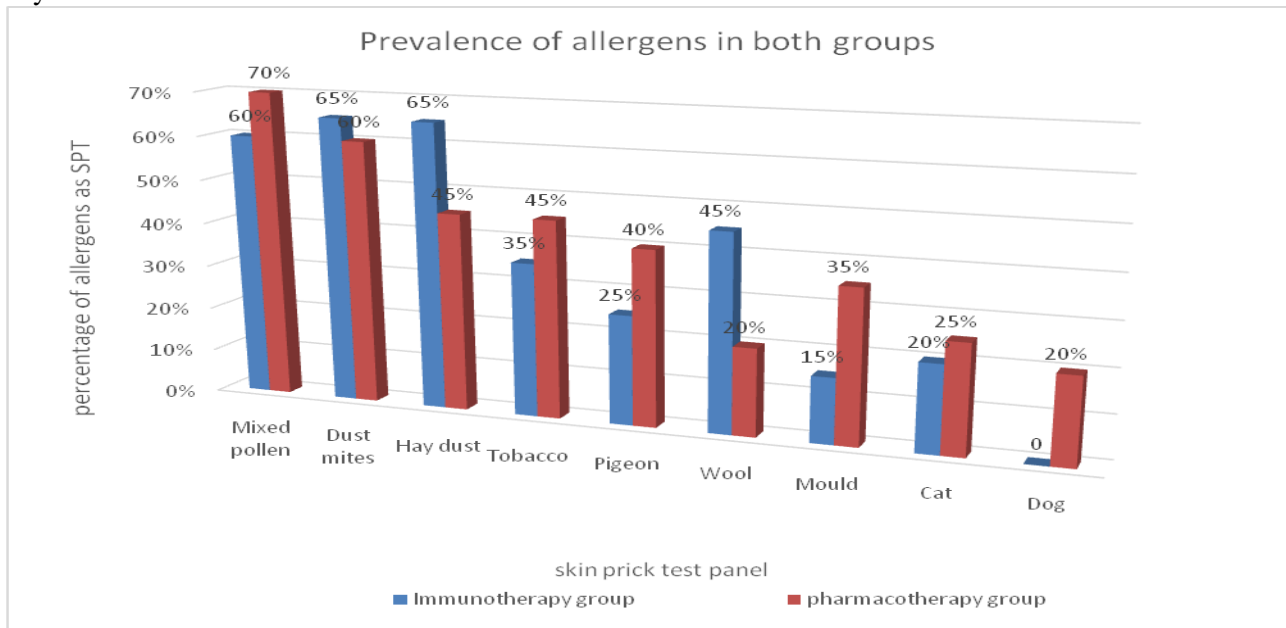


Figure (1): Prevalence of allergens positivity in the study subjects

Table (2) showed that there was no statistically significant difference between the studied groups regarding baseline quality of life score and total nasal symptoms score before start of immunotherapy.

Table (2): Comparison between the studied groups regarding quality-of-life questionnaire score and total nasal symptoms score before the start of immunotherapy

	Immunotherapy group Mean ± SD	Pharmacotherapy group Mean ± SD	T	P
Baseline Quality of life Questionnaire score	69.8 ± 8.95	67.95 ± 7.97	0.69	0.494
Baseline Total Nasal Symptoms score	9.55 ± 1.32	9.5 ± 1.64	0.106	0.916

t-independent sample t test

Table (3) showed that the quality of life score started to show significant improvement after five weeks of start of immunotherapy for immunotherapy group and this improvement continued till the end of six months therapy.

Table (3): Quality of life Questionnaire score follow up of the two groups during six months study period

	Immunotherapy group Mean ± SD	Pharmacotherapy group Mean ± SD	T	p
(Start of immunotherapy)				
Week 1	69.7 ± 8.8	68.0 ± 7.98	0.64	0.526
Week 2	71.25 ± 7.02	68.25 ± 7.67	1.205	0.236
Week 3	69.2 ± 7.52	67.7 ± 8.36	0.596	0.554
Week 4	66.85 ± 8.12	67.55 ± 8.62	-0.264	0.793
Week 5	63.95 ± 9.24	67.0 ± 8.65	-1.078	0.288
Week 6	61.15 ± 8.07	67.0 ± 8.52	-2.23	0.032*
Week 7	59.1 ± 8.18	66.85 ± 8.02	-3.026	0.004*
Week 8	56.9 ± 7.93	67.9 ± 7.14	-4.61	<0.001**
Week 9	53.75 ± 7.21	67.55 ± 6.86	-6.2	<0.001**
Week 10	50.25 ± 5.97	67.0 ± 6.4	-8.558	<0.001**
Week 11	49.25 ± 6.71	65.55 ± 6.54	-7.778	<0.001**
Week 12	46.5 ± 6.32	65.2 ± 6.21	-9.437	<0.001**
Week 13	44.0 ± 6.02	65.85 ± 6.55	-10.988	<0.001**
Week 14	41.6 ± 6.41	66.15 ± 6.95	-11.616	<0.001**
Week 15	39.15 ± 6.13	65.6 ± 6.67	-13.057	<0.001**
Week 16	36.85 ± 6.76	64.8 ± 6.86	-12.793	<0.001**
Week 17	34.3 ± 6.62	63.75 ± 5.76	-15.014	<0.001**
Week 18	31.25 ± 6.87	64.0 ± 6.05	-15.992	<0.001**
Week 19	27.45 ± 8.19	63.95 ± 4.89	-17.117	<0.001**
Week 20	24.55 ± 8.99	62.9 ± 4.61	-16.978	<0.001**
Week 21	22.35 ± 8.71	63.2 ± 5.07	-18.118	<0.001**
Week 22	19.75 ± 8.56	63.0 ± 5.65	-18.863	<0.001**
Week 23	17.25 ± 8.3	63.3 ± 5.87	-20.256	<0.001**
Week 24	16.05 ± 8.11	63.2 ± 5.17	-21.265	<0.001**

t independent sample t test

Figure (2) showed the significant improvement in the total nasal symptoms (TNS) score of the group treated with immunotherapy than in that treated with pharmacotherapy alone.

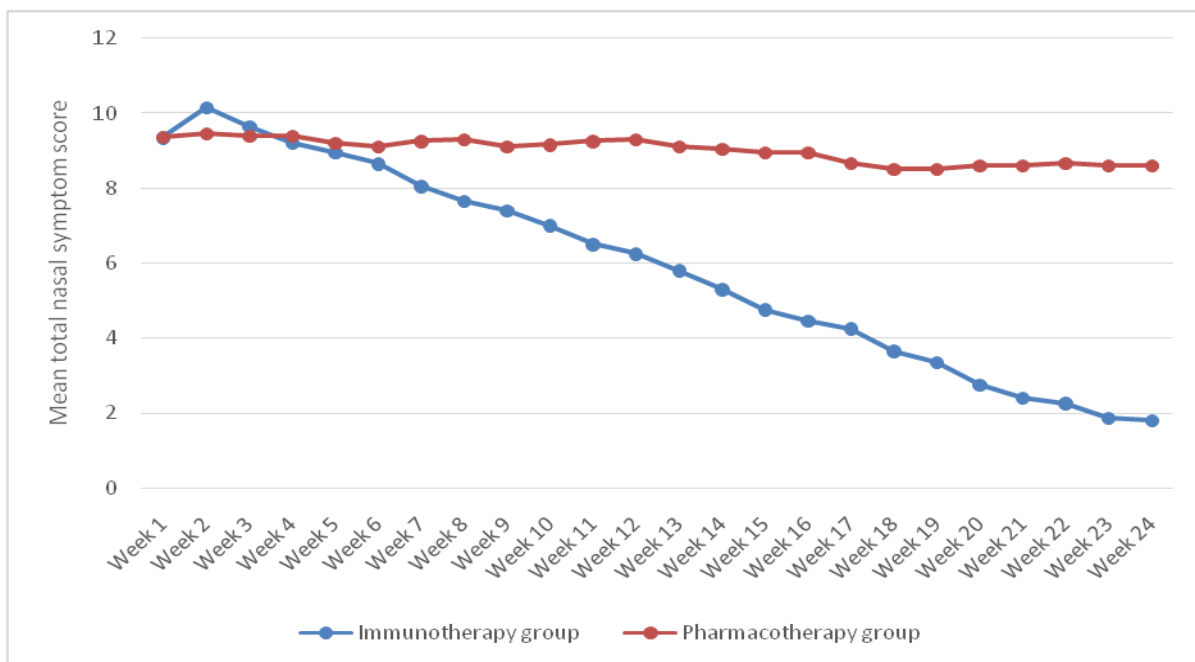


Figure (2): Multiple line graph showing total nasal symptoms (TNS) score (mean) for both groups during the six months study period.

Table (4) showed the significant improvement in quality of life questionnaire score and in total nasal symptoms score among the immunotherapy group with a percentage of 77.97% and 81.67% respectively.

Table (4) :Percentage of improvement in both quality-of-life Questionnaire score and Total Nasal Symptoms (TNS) Score by the end of six months study period in studied groups

	Immunotherapy group Median (IQR)	Pharmacotherapy group Median (IQR)	Z	p
Quality of life Questionnaire score	77.97(71.43 – 87.01)	4.4(-1.07 – 13.13)	-5.412	<0.001**
Total Nasal Symptoms (TNS) score	81.67(70.36 – 90)	4.17(0 – 15.63)	-5.436	<0.001**

Z Mann Whitney test

As regards the total nasal symptoms score, there was a statistically significant positive correlation between patient age and the percentage of improvement (Figure 3).

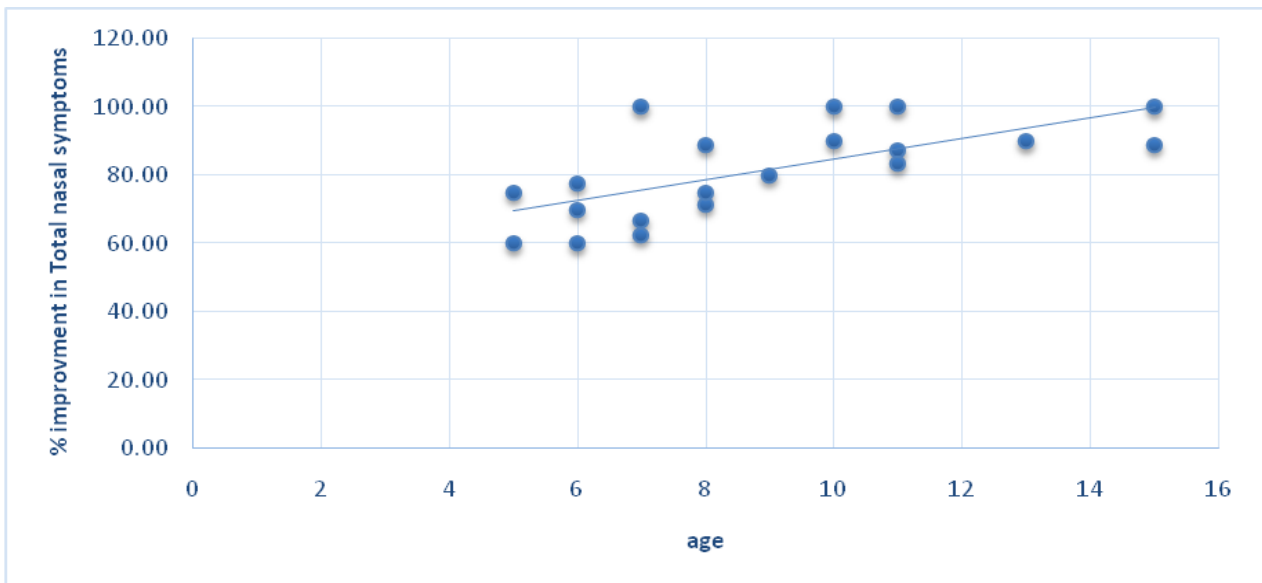


Figure (3): Scatter dot plot showing significant positive correlation between age and percentage of improvement in Total nasal symptoms among immunotherapy group.

Table (5) showed that there was statistically significant relation between percentage of improvement in quality of life questionnaire score and seasonality (Perennial Allergic Rhinitis was associated with better improvement).

Table (5): Factors affecting percentage of improvement in quality of life Questionnaire score among immunotherapy group

	Median (IQR)		Z	p
Severity	Moderate	Severe	-0.371	0.71
	77.97(71.57 – 87.58)	77.93(66.29 – 86.57)		
Seasonality	Seasonal	Perennial	-2.105	0.033*
	71.96(66.29 – 85)	86.16(80.58 – 92.26)		
Asthma:	Negative	Positive	-0.756	0.449
	77.97(71.43 – 87.3)	70.66(57.91 – 84.52)		
Dermatitis	Negative	Positive	-0.039	0.97
	72.46(68.63 – 87.68)	83.45(71.48 – 85.75)		
Conjunctivitis:	Negative	Positive	-0.315	0.753
	77.97(71.43 – 87.3)	77.98(71.43 – 84.52)		

By the end of the study, there was statistically significant difference between the studied groups regarding nose, practical symptoms, activities and abstinence days from school (Significantly lower in immunotherapy group).

Within Immunotherapy group, there was significant improvement in nose, practical symptoms, and abstinence days by the end of the study (Table 6).

Table (6): Comparison between the studied groups regarding domains of quality of life questionnaire at the start (before beginning in immunotherapy) and by the end of the study

	Immuno-therapy group N=20 (%)	Pharmacotherapy group N=20 (%)	Z	P
	Median (IQR)	Median (IQR)		
Nose symptoms domain:	6(5 – 6)	5.5(5 – 6)	-0.947	0.343
At start	0(0 – 1)	5.5(5 – 6)	-5.463	<0.001*
by the end				*
P(Wx)	<0.001**	0.527		
Practical symptoms domain:	5.5(5 – 6)	6(5 – 6)	-0.313	0.755
At start	1(1 – 2)	5.5(5 – 6)	-5.186	<0.001*
by the end				*
P(Wx)	<0.001**	0.18		
Activities domain:	6(6 – 6)	6(6 – 6)	0	>0.999
At start	1.5(1 – 2)	6(6 – 6)	-5.634	<0.001*
by the end				*
P(Wx)	<0.001**	0.317		
Abstinence (day/month)	6(4 – 7)	6(6 – 7)	-1.409	0.149
At start	1.5	5.5(5 – 7)	-5.333	<0.001*
by the end	(0.25 – 2)			*
P(Wx)	<0.001**	0.016		

Wx Wilcoxon signed rank test

In the first week, one patient within immunotherapy group had redness, while in second week, one patient had subcutaneous swelling. In the third week, one patient had redness and hotness and one patient in fourth week had subcutaneous swelling. After that, no patient was complicated. Four patients (20%) developed adverse reactions to injections within immunotherapy group in the form of local mild reactions (Table 7).

Table (7): Adverse reactions developed on immunotherapy

	Immunotherapy group N=20
Week 1	1 (Redness)
Week 2	1 (Subcutaneous swelling)
Week 3	1 (Redness, hotness)
Week 4	1 (Subcutaneous swelling)

DISCUSSION

Allergy rhinitis affects the nasal passages and is very common. Its incidence differs in different parts of the world. Twenty percent to thirty percent of adults and up to forty percent of children, according to a

credible epidemiological study. Since AR is linked to several problems and comorbidities like asthma, otitis media, sinusitis, nasal polyps, and lower respiratory tract infections, going untreated can have devastating effects, especially among children ⁽¹¹⁾.

Subjects with allergic rhinitis (AR) with or without allergic asthma can benefit from allergen immunotherapy (AIT) in either the subcutaneous (SCIT) or sublingual (SLIT) route. A major challenge for pediatricians has always been SCIT. However, there is substantial proof of effectiveness. Children, however, always demonstrate more robust resistance when injected with SCIT. As an additional side effect (SE) of SCIT, people frequently experience upper respiratory tract infections that manifest similarly to allergy symptoms ⁽¹²⁾.

To eliminate the contribution of any confounding factor that may affect the final outcome the current study enrolled two well-matched groups in baseline data, as there was no statistically significant difference between the studied groups as regards demographics and baseline QoL.

In the current study, the most common allergens found among study subjects were mixed pollens, Dust mites and Hay Dust.

Regarding quality-of-life questionnaire score follow up, it was revealed that the quality-of-life score started to show significant improvement after five weeks of start of immunotherapy for immunotherapy group and this improvement continued till the end of six months therapy.

Also, there was significantly higher improvement in the quality of life of the immunotherapy-treated group than that treated with pharmacotherapy alone.

The comparison between the studied groups regarding domains of quality-of-life questionnaire at the start (before beginning in immunotherapy) and by the end of the study showed that by the end of the study there was statistically significant difference between the studied groups regarding nose, practical symptoms, activities and abstinence days from school (Significantly lower in Immunotherapy group).

Within Immunotherapy group, there was significant improvement in nose, practical symptoms, activities, and abstinence days by the end of the study. This is in agreement with **Bozek et al.** ⁽¹³⁾ Patients' baseline characteristics that were similar across the immunotherapy and control groups in their randomised-controlled trial. The study found that while both groups' QoL scores were comparable at the outset, the Immunotherapy group's QoL scores declined considerably after three years of AIT therapy (p =.03) while the control group's QoL scores were unaffected. Also, in line with **Agenäs et al.** ⁽¹⁴⁾ study, which involved 158 kids aged 5 to 16, who looked at how pollen subcutaneous immunotherapy (SCIT) affected their health-related quality of life (HR-QoL) over the course of three years. The results showed that

after 1 year of pollen SCIT, HR-QoL was considerably improved ($p < 0.001$) and was stable until the last follow-up 3 years later. As well, **Lin et al.** ⁽¹⁵⁾ observational study. Authors assessed the efficacy of SCIT in 225 AR-afflicted kids aged 4-17. Quality of life increased after SCIT was administered, and it remained higher than it was at the study's outset. In addition, a meta-analysis of randomized controlled trials by **Zhu et al.** ⁽¹⁶⁾ included a total of 134 participants over 4 publications found that the SCIT group improved on quality-of-life questionnaires significantly than the placebo group.

Regarding total nasal symptoms (TNS) score follow-up, the current study revealed that TNS Score started to show significant improvement after six weeks of start of immunotherapy for immunotherapy group and this improvement continued till the end of six months therapy. The improvement in TNS score of the group treated with immunotherapy was significantly higher than that treated with pharmacotherapy alone. In agreement with the current study, **Bozek et al.** ⁽¹³⁾ showed that three years into AIT, the immunotherapy group's symptoms score had greatly improved, but the control group's score had not changed at all. As well, **Ünal** ⁽¹⁷⁾ showed that the AIT group showed clinical improvement in AR symptoms, while the usual medication group showed no difference in nasal symptoms. Also, **Lin et al.** ⁽¹⁵⁾ evaluated clinical symptoms using a visual-analogue-score (VAS) and significant improvements were seen beginning 4 months into SCIT as compared to baseline and continuing throughout the research. Similarly, **Ren et al.** ⁽¹⁸⁾ showed that SCIT showed a substantial reduction in the total nasal symptom score (TNSS) at three years following treatment initiation and at the most recent follow-up (more than three years).

The comparison of percentage of improvement in both quality-of-life questionnaire score and TNS score by the end of six months study period in studied groups, showed that there was significant improvement in quality-of-life questionnaire score and in TNS score among the immunotherapy group with a percentage of 77.97% and 81.67% respectively. However, the improvement in quality-of-life questionnaire score and in TNS score among the control group with a percentage 4.4% and 4.17% respectively. In agreement with the current study, the meta-analysis by **Zhu et al.** ⁽¹⁶⁾ showed that The SCIT group showed a greater increase in QoL and symptom score questionnaire improvement than the placebo group did. Comparable with the current study **Lourenço et al.** ⁽¹⁹⁾ among 281 individuals with AR enrolled (ranging in age from 3 to 69), the majority (65%) were children and adolescents, and the results showed that SCIT significantly reduced the severity of AR symptoms.

Regarding the correlation between age, disease duration, and total IgE and percentage of improvement with both quality-of-life questionnaire and TNS scores among immunotherapy group, there

was a statistically significant positive correlation between patient age and the percentage of improvement of TNS scores. However, there was no significant correlation between the improvement percentage of QoL and the studied parameters. The idea that SCIT administered to children with AR at a younger age would be more effective is now widely held on the theory that the immune system might respond better to the treatment during its formative years ⁽²⁰⁾, which support our findings. This was supported by **Agenäs et al.** ⁽¹⁴⁾ who found that after a year of treatment, younger children's perceptions of their physical ability were higher than those of older children (79.4 vs. 71.3, $p=0.01$). In terms of quality of life, there was no discernible difference between the young and the old. However, **Lin et al.** ⁽¹⁵⁾ showed that children older in age (OR=0.688, 95% CI: 0.479-0.988) and those with a history of allergies (OR=0.097, 95% CI: 0.009-1.095) had a reduced chance of ineffective treatment.

We also assessed factors affecting percentage of improvement in quality-of-life questionnaire score among immunotherapy group, there was statistically significant relation between percentage of improvement in quality-of-life questionnaire score and seasonality (Perennial Allergic Rhinitis was associated with better improvement). This is supported by **Pfaar et al.** ⁽²¹⁾ who stated that outcomes in AIT are particularly affected by fluctuations in natural exposure (e.g., seasonality) and the natural history and severity of the disease. In agreement with the current study **Tworek et al.** ⁽²²⁾ concluded that perennial is more effective than preseasonal subcutaneous immunotherapy in the treatment of seasonal allergic rhinoconjunctivitis. However, **Sözener et al.** ⁽²³⁾ results showed that preseasonal immunotherapy significantly improved symptom management during the whole pollen season. However, among those receiving perpetual immunotherapy, the blocking antibody response was both more robust and long-lasting.

Regarding adverse reactions developed on immunotherapy, it was revealed that in the first week, one patient within immunotherapy group had redness, while in second week, one patient had subcutaneous swelling. In the third week, one patient had redness and hotness and one patient in fourth week had subcutaneous swelling after that no patient was complicated. Four patients (20%) developed adverse reactions to injections within immunotherapy group in the form of local mild reactions.

However, **Bozek et al.** ⁽¹³⁾ showed that neither group experienced any serious anaphylactic reactions during the AIT treatment. In the AIT group, 101 injections (21.8%) resulted in erythema or wheals 5 cm, and 28 injections (9.5%) resulted in wheals > 5 cm. In the group given a placebo, there were no reported side effects. While, **Lourenço et al.** ⁽¹⁹⁾ showed that a total of 281 AR patients who were given AIT showed no signs of adverse response or reactions.

CONCLUSION

The current study showed that subcutaneous immunotherapy was safe and effective in the treatment of allergic rhinitis in children. It resulted in significant improvement in QoL and symptoms through the study period, and this improvement was higher than the pharmacotherapy only group. Subcutaneous immunotherapy was associated with minor adverse events. Younger patient age was found to be associated with better improvement in symptoms, also, perennial allergic rhinitis was associated with better improvement in both QoL and symptoms.

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Competing interests: Nil.

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