Does immunotherapy reduce the recurrence rate in nasal polyposis?

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Background
Nasal polyposis (NP) is a chronic inflammatory condition with no proved effective long-term treatment and a tendency to recur.

Aim
The aim of our study was to evaluate the effect of immunotherapy on the recurrence rate of NP in atopic patients after surgical management and the ability to improve the quality of patients' lives and decrease their suffering.

Patients and methods
We chose 60 patients (discussion with the patients with respect to the benefits and hazards of the study was performed and informed consents were provided) with bilateral NP (as diagnosed by full history taking, clinical examination, nasal endoscopic examination, and sinonasal computed tomography) who proved to be allergic (by full history taking, clinical examination, skin prick test, serum total IgE, serum-specific IgE). We classified them into three groups: group I included 18 patients who underwent surgical management (functional endoscopic sinus surgery) as a control group, group II included 18 patients who underwent treatment with subcutaneous immunotherapy by gradual up-dosing protocol for inhalant allergens as a second control group, and group III included 20 patients who underwent treatment with subcutaneous immunotherapy for inhalant allergens 6 weeks after surgical treatment.

Results
In the three groups of patients, the sinoNasal Outcom -22 (SNOT-22) scores were significantly decreased (with the minimally important difference greater than 9 points in 17/18 patients in group I, 17/20 patients in group III, and 15/18 patients in group II), denoting significant clinical improvement in the three groups. However, patients treated with surgery and postsurgical immunotherapy reported more improvement, with no significant difference between them, than those treated with immunotherapy alone. Seven (38.9%) patients of group I had recurrence of NP, whereas six (30%) patients of group III had recurrence. On comparison, there was no statistically significant difference between the two groups. In group II, the NP score was declined on immunotherapy alone but did not disappear completely. The timing of recurrence of NP in patients of group I ranged from 7 to 13 months, whereas in group III it ranged from 12 to 16 months.

Conclusion
We found that immunotherapy could help in improving patients' clinical symptoms and subsequently their quality of life; postoperative immunotherapy in addition can delay the recurrence, although it does not decrease the recurrence rate significantly.

Keywords:
allergy, immunotherapy, polyposis

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Introduction

Nasal polyposis (NP) is a chronic, largely unknown condition with no effective long-term treatment and a tendency to recur [1].

The incidence of allergy in patients with NP has been found to range from 10 to 96.5% depending on the study [2,3]. Increased eosinophil counts and elevated levels of local total and specific immunoglobulin E (IgE) are measured in nasal polyps, and in most studies the number of degranulating epithelial mast cells in nasal polyps is high [4]. Allergen-specific immunotherapy is recommended by the WHO as an integrated part of allergy management strategy [5]. It is recognized as a highly effective practice in the treatment of patients with severe allergic rhinitis and/or asthma.

Sinus surgery, currently referred to as functional endoscopic sinus surgery (FESS), is a standard treatment with good functional results in patients resistant to medical treatment. Extensive postoperative care and long-term follow-up are required to preserve the postoperative results and to prevent regrowth of polyps [1].

Regardless of a medical or surgical approach to treatment, most polyps do recur [6], with varied postoperative recurrence rate results ranging from 13 to 75% [7].

The high recurrence rate of NP after both effective medical and surgical treatment and the lack of a definite proven treatment modality proven by randomized controlled studies had stimulated us to perform this study.

Aim

The aim of the study was to analyze and evaluate the effect of immunotherapy on the NP, mainly on post-treatment recurrence rates, through a prospective randomized controlled trial.

Patients and methods

This study was conducted in both ENT Department and Allergy and Clinical Immunology Unit, Internal Medicine Department, Ain Shams University, from September 2009 to March 2012.

The study was approved by the Research Ethical Committee of the Faculty of Medicine, Ain Shams University.

Patients

Discussion with the patients with respect to the benefits and hazards of the study was performed and informed consents were obtained.

A total of 60 patients with bilateral NP were enrolled in the study after informed consent about the research and the procedures (specified for each group) has been taken. They were randomly classified into three groups:

(1) Group I (18 patients): this group included 20 patients who underwent FESS only, with two patients who did not complete the follow-up period due to noncompliance.
(2) Group II (18 patients): this group included 20 patients who were treated with immunotherapy only, with two patients who stopped immunotherapy due to aggravation of chest condition.
(3) Group III (20 patients): this group included patients who were treated with postoperative immunotherapy.

Inclusion criteria

Patient with bilateral polyposis who:

(1) Have allergic etiology (on the basis of history, skin prick testing (SPT), total IgE, and serum and/or tissue-specific IgE).
(2) Are not responding to medical treatment in the form of the following:
    (a) One month with systemic steroids in the form of (prednisolone tablets) full dose (2 mg/kg/day) tapered over 3 weeks.
    (b) Topical steroids (budesonide nasal spray) for at least 4 weeks.
    (c) Antibiotics according to the guidelines for at least 2 weeks.
    (d) Antileukotrienes and antihistamine according to case.

Exclusion criteria

(1) Nonallergic polyps (such as antrochoanal, cystic fibrosis, etc.).
(2) Patients with negative results for the three allergy tests (SPT, serum specific IgE, and tissue specific IgE).
(3) Generalized skin allergy, severe dermatographism, and severe asthma.
(4) Patients with immunological disorders (autoimmune diseases).

Methods

All patients were subjected to the following:

(1) Full medical and ENT history taking and clinical examination and history of allergic diseases were obtained, and SNOT-22 test questionnaire was obtained from each patient with respect to nasal symptomatology and the quality of life at the beginning of the study [8].
(2) ENT examination.
(3) Nasal endoscopy: grading of NP was recorded (1 month after maximum effective medical therapy) according to the Lund–Mackay staging of NP [9].
(4) Nonenhanced CT-PNS: grading of NP was recorded according to the Lund–Mackay computed tomography (CT) staging of NP [9].
(5) Diagnostic allergic workup:
    (a) SPT: the panel of allergen extracts were prepared in Allergen Extract Unit, Department of Allergy and Immunology, Ain Shams University Hospitals. They were prepared by aqueous vaccine method (weight/volume) [10]. The panel for skin testing was composed of histamine and saline, in addition to 37 different allergen extracts for both inhaled and ingested allergens.

(b) Serum total IgE level: enzyme-linked immunosorbent assay was used for the quantitative determination of IgE concentration in human serum (BioChech IgE Enzyme Immunoassay; BioCheck Inc., Foster City, California, USA) [11].
(c) Serum-specific IgE: enzyme-linked immunosorbent assay was used for the quantitative determination of circulating allergen-specific IgE in human serum [RIDASCREEN Spezifisches IgE (A0249); R-Biopharm AG, Darmstadt, Germany] [11].
(d) Tissue-specific IgE: the tissues were homogenized with a mechanical homogenizer (B. Braun, Melsungen, Germany), centrifuged, and separated. Supernatants were assayed for specific IgE levels using enzyme immunoassay for the quantitative determination of allergen-specific IgE as performed in human serum [11].

Patients of groups I and III underwent FESS.

(1) Patients underwent standard FESS in ENT Department, Ain Shams University.
(2) Standard FESS aimed at restoring normal sinus function and ventilation without excessive removal of potentially reversibly diseased tissue [12].

Patients of group II and III after FESS were subjected to immunotherapy.

Technique and schedules of immunotherapy:

The allergens vaccines used for subcutaneous immunotherapy (SCIT) were prepared in Allergen Extract Unit, Department of Allergy and Immunology, Ain Shams University Hospital. The vaccines were prepared by aqueous vaccine method (weight/volume) [10].

Immunotherapy was given by the conventional gradual up-dosing protocol consisting of two phases, namely initiation and maintenance. The initiation kit comprised three vials of different dosage concentrations: 1/10 000, 1/1000, and 1/100. Patients received increasing doses starting with 0.2 ml from the first vial (1/10 000). The dose was increased by 0.2 ml every 3 days (twice weekly injections). When a dosage of 1 ml injection was reached, the same process was repeated every week for the next month. The second vial (1/1000) was started following the same regimen followed by the third vial (1/100) as well.

When a dosage of the third vial is completed, maintenance therapy, consisting of 1 ml injection of 1/100 concentration, was given every week until the end of the 18-month period. Patients were instructed to take a tablet of antihistamine 2 h before each injection [13].

At the end of follow-up period (18 months):

(1) Nasal endoscopic examination was performed and the final score was recorded.
(2) A questionnaire of SNOT-22 test was administered to every patient at the end of final study visit.
(3) CT-PNS was performed at the end of follow-up period.

Statistical analysis

Statistical analysis was performed on a personal computer using the IBM SPSS statistics (version 20; IBM Corporation, Armonk, New York, USA) software.

Results

There was no statistically significant difference detected between the three groups with respect to age and sex, positive family history to allergy, and positive history of bronchial asthma (BA) ($P > 0.05$) (Table 1).

There was clinical improvement (SNOT-22 results) with a statistically significant difference between results before and after intervention for each of the three groups ($P < 0.001$). On comparison between the three studied groups, there was a statistically significant difference between group I and group II and a statistically significant difference between group III and group II. However, there was no statistically significant difference between group I and group III.

The most common annoying presentation for all patients was 'nasal blockage and congestion' with the highest grand total score of 210, followed by

Table 1 Comparison between the studied groups with respect to the general data

Variables	*n* (%)					
	All patients (*n* = 56)	Group I (*n* = 18)	Group II (*n* = 18)	Group III (*n* = 20)	*F*	*P* value
Age	33.4 ± 3	33.3 ± 2	34 ± 4	32 ± 3	1.1	>0.05
Sex						
Male	22 (39.3%)	7 (38.9)	6 (33.3)	9 (45)	0.5	>0.05
Female	34 (60.7)	11 (61.1)	12 (66.7)	11 (55)		
Positive family history	31 (55.4)	7 (38.9)	11 (61.1)	13 (65)	2	>0.05
Positive history of BA	20 (35.7)	8 (44.4)	6 (33.3)	6 (30)	0.9	>0.05

'embarrassment' with a grand total score of 184, and 'decreased sense of taste and smell' with a grand total score of 184.

The χ^2-test was used to evaluate the finding and showed a significant difference between all groups after intervention with respect to nasal blockage and congestion (Table 2) and also with respect to embarrassment (data not shown). There was no statistically significant difference between the three groups after intervention with respect to sense of smell and taste (Table 3).

We chose another two items (sneezing and postnasal discharge) of SNOT-22 test as allergy-related symptoms to assess the clinical improvement of patients before and after intervention. There was a statistically significant difference between all groups after intervention with respect to sneezing (Table 4) postnasal discharge (data not shown).

On comparison of endoscopic assessment results between the three studied groups, there was a statistically significant difference between group I and group II and a statistically significant difference between group III and group II. However, there was no statistically significant difference between group I and group III.

With respect to SPT, 15 (26.8%) patients showed negative results to SPT and 41 (73.2%) patients showed positive results to SPT, with six (14.6%) patients showing positive result to only one allergen (monosensitized), whereas the remaining patients were polysensitized. The most common allergens found to be positive by SPT were: 'house dust' with positive results in 19 patients representing 46.3% of patients with positive results to SPT (41 patients), followed by 'pollens' with positive results in 18 (43.9%) patients, 'house dust mite' with positive results in 17 (41.5%) patients, and then 'molds' with positive results in 14 (34.2%) patients.

On comparison of the decline in CT score results between the three studied groups, there was a statistically significant difference between group I and group II and a statistically significant difference between group III and group II. However, there was no statistically significant difference between group I and group III.

With respect to serum total IgE, there was no statistically significant difference between the three studied groups ($P > 0.05$) (Table 5).

All our 56 patients had positive total IgE (>100 IU/dl). However, 91.1% (51/56) patients had positive serum-specific IgE (>0.35 IU/dl) and 'the five patients with negative results showed positive SPT results', whereas 100% (56) patients had positive tissue-specific IgE (>0.35 IU/dl) for the tested allergens. The most common allergens found to have positive results in both serum-specific and tissue-specific IgE were pollens, house dust, house dust mite, and molds, which are the same common allergens found by SPT.

Table 2 Comparison of nasal blockage/congestion score before and after intervention between the studied groups (χ^2-test)

Variables	Group I (n = 18)		Group II (n = 18)		Group III (n = 20)		χ^2	P value
	Total	Median	Total	Median	Total	Median		
Nasal congestion before intervention	72	4 (4–4)	69	4 (3–5)	69	3 (3–4)	5.6	<0.05
Nasal congestion after intervention	22	1 (0–2)	36	2 (1–3)	26	1 (0–2)		
Improvement (%)	69.4		47.8		62.3			

Table 3 Comparison of sense of smell/taste score before and after intervention between the studied groups (χ^2-test)

Variables	Group I (n = 18)		Group II (n = 18)		Group III (n = 20)		χ^2	P value
	Total	Median	Total	Median	Total	Median		
Smell/taste before intervention	59	3 (3–4)	60	3 (2–5)	65	3 (3–4)	3	>0.05
Smell/taste after intervention	35	2 (1–3)	39	2 (1–3)	31	2 (1–2)		
Improvement (%)	40.7		35		52.3			

Table 4 Comparison of sneezing score before and after intervention between the studied groups (χ^2-test)

Variables	Group I (n = 18)		Group II (n = 18)		Group III (n = 20)		χ^2	P value
	Total	Median	Total	Median	Total	Median		
Sneezing before intervention	38	3 (1–3)	39	2 (1–3)	47	2 (2–3)	6.8	<0.05
Sneezing after intervention	17	1 (0–2)	10	0.5 (0–1)	9	0 (0–1)		
Improvement (%)	55.3		74.4		80.9			

Table 5 Comparison between the studied groups with respect to total immunoglobulin E

Variables	Group I (n = 18)	Group II (n = 18)	Group III (n = 20)	F	P value[a]
Mean ± SD	159 ± 37	164.6 ± 38	188.6 ± 48	2.6	>0.05
Range	106–224.5	107.5–243	113–273		

[a]Comparison between the studied groups as regard total IgE

Minor intraoperative complications (minor bleeding and other minor complications) were managed intraoperatively. No major complications of surgery were recorded intraoperatively or postoperatively during the follow-up period. SCIT complications included two (5%) patients who experienced increase in the severity and frequency of BA attacks that necessitated cessation of treatment with immunotherapy. No major complications were recorded. In all, 7.5% (3/40) of patients had mild increase in frequency of BA attacks, which was managed by modifying the medical treatment of BA; 42.5% (17/40) of patients had local allergic reaction at the site of injection in the form of skin indurations and itching, which was managed by oral antihistamine intake before each injection and by applying cold foments at the site of injection; and 15% (6/40) of patients had mild generalized body itching, which was managed by slight modification of doses through repetition of the last two doses with a slower and longer course until reaching the dose that causes itching again. There was no itching reported after modifying the dose.

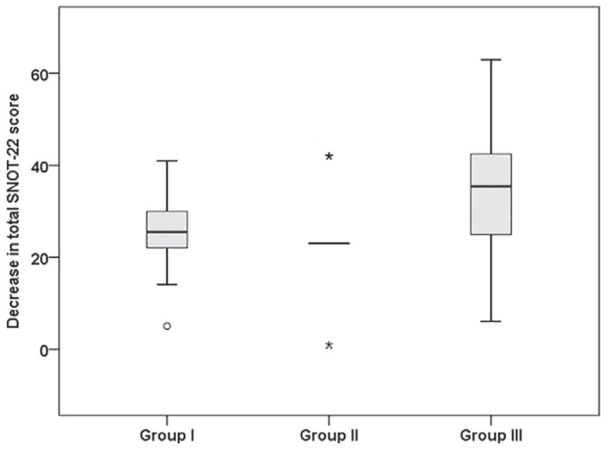
Recurrence of NP was determined by nasal examination and nasal endoscopy scoring. Seven patients of group I had recurrence of NP representing 38.9% of patients, whereas six patients of group III had recurrence representing 30% of patients. On comparison, there was no statistically significant difference between the two groups. With respect to group II, the NP score was declined on immunotherapy alone but did not disappear completely.

Timing of recurrence of NP in patients of group I ranged from 7 to 13 months. However, recurrence of NP in patients of group III ranged from 12 to 16 months. The median time to recurrence could not be determined in either group, as more than 50% of patients were free of recurrence by the end of the study.

Discussion

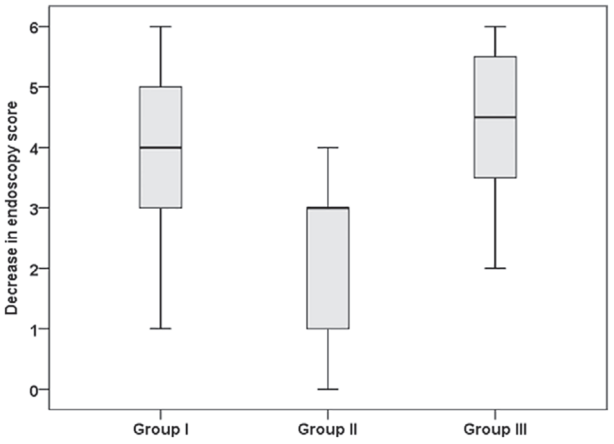
In 90% of NPs, eosinophils comprise the most prevalent inflammatory cell type. These cells have a demonstrable ability to synthesize and release mediators and powerful regulatory molecules. This marked self-perpetuating eosinophilia and the noted

Figure 1



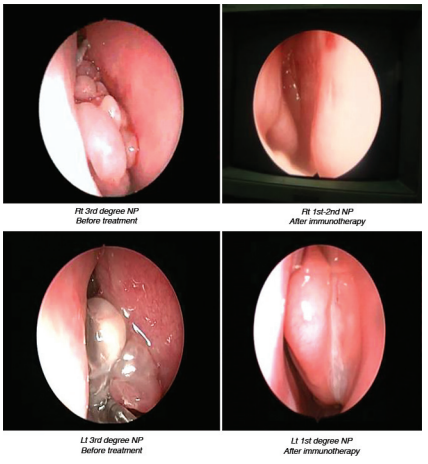
Difference in total SNOT-22 scores in the three study groups.

Figure 2



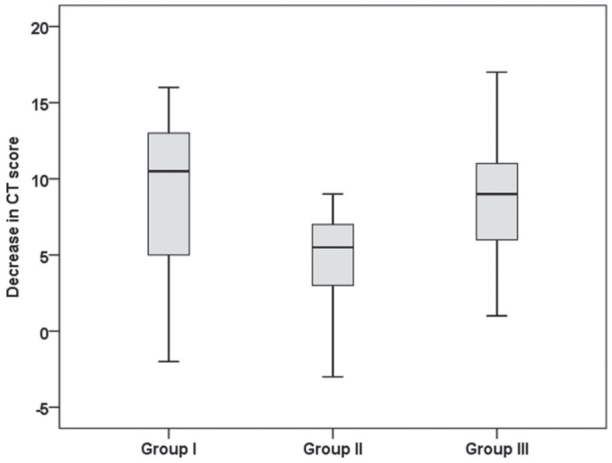
Difference in endoscopy scores in the three study groups.

Figure 3



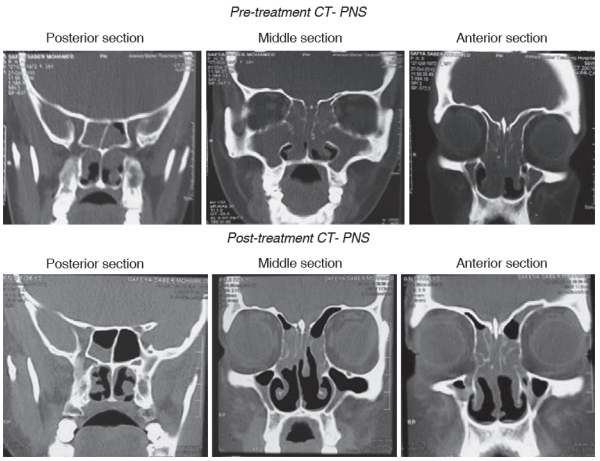
Nasal endoscopy of patient no. 21, group II, before and after treatment with postoperative immunotherapy. NP, nasal polyposis.

Figure 4



Difference in computed tomography (CT) scan scores in the three studied groups.

Figure 5



Computed tomography (CT) demonstration of patient no. 21, group II, before and after management with immunotherapy only.

association with atopic states have led to allergy being implicated in the pathogenesis of NP [14].

In the present study, the mean age was 33.4 years, with 22/56 male patients representing 39.3% and 34/56 female patients representing 60.7%. In a study conducted by Larsen and Tos [15] on the incidence of NP, they found that NPs are uncommon under the age of 20 years and are more frequently found in men than in women. The incidence increased with age, reaching peaks in the age group of 50–59 years. Klossek *et al*. [16] found that NPs occur in all races and become more common with age. The average age of onset is ~42 years. These differences between our study and the previous studies are due to our small randomized sample; in addition, we chose atopic patients only.

In the present study, bronchial asthma was the most prevalent pathological entity among the patients. We found 20/56 (35.7%) patients who had previously been diagnosed as asthmatic. Our results were consistent with previous studies conducted by Munoz Del Castillo *et al*. [2]; they found that 42.6% of the patients with NP had previously been diagnosed as asthmatic. In addition, Klossek *et al*. [16] found that wheezing and respiratory discomfort are present in 31–42% of patients with NP, and asthma is reported by 26% of patients with NP compared with 6% of controls.

In the present study, the most common allergen with positive results in SPT was 'house dust' with positive results in 19/41 (46.3%) patients followed by 'pollens' with positive results in 18/41 (43.9%) patients. Some studies such as the study by Demoly *et al*. [17] conducted in 2000 revealed extensive sensitization (80% of patients with NP) especially to House dust mite, which is a much higher percentage than that observed in our study, 17/41 (41.5%) patients.

A study conducted by Krouse [18] shows that 22.4% of patients with NP with allergy signs and symptoms had positive IgE to some fungal allergen [2]. In our study, the prevalence of fungal allergies among the SPT-positive patients was 46.3% (19/41). The fungal allergens that most commonly elicited a reaction in the SPT were a mixture of fungal allergens 'mixed molds' positive in 14/41 (34.2%). *Aspergillus fumigatus* was positive in 8/41 (19.5%) and *Rhyzopus* in 8/41 (19.5%). In 2000, a study conducted by Asero and Bottazi [19] found that 40% of patients tested were positive to *Candida albicans*. Our results show that only 12.2% (5/41) patients were positive to *C. albicans*.

In the three groups of patients, the SNOT-22 scores were significantly decreased (with the minimally important difference >9 points in 17/18 patients in group I, 17/20 patients in group III, and 15/18 patients in group II), denoting significant clinical improvement; this means that the three applied management modalities of NP are efficient in controlling the patients' symptoms and affording clinical improvement. However, patients treated with surgery and postsurgical immunotherapy reported more improvement, with no significant difference between them, than those treated with immunotherapy alone.

An interesting result was found regarding patients treated with immunotherapy alone after completion of the follow-up period; six (33.3%) patients were completely satisfied by their improvement and needed no surgical interference. However, six (33.3%) patients were not satisfied by the result and requested for surgical interference. Rest of the patients (33.3%)

reported moderate satisfactory improvement and preferred to postpone surgery.

There was a significant improvement interpreted by the decline of the endoscopic staging and CT scoring within the three groups of patients after different treatment modalities, which correlate with the clinical improvement reported by the patients. This improvement was greater in patients treated with FESS and in those treated with postsurgical immunotherapy.

The improvement of CT scores in groups I and III could be attributed to surgical elimination of the diseased mucosa, whereas the improvement of CT scores in group II could be explained by decreased inflammatory mediators by the action of immunotherapy.

Staikūnienė *et al*. [20] supported our finding; they found a positive correlation between sinus CT scans and blood eosinophilia but not total IgE. The results showed a trend toward positive correlation between sinus CT stage and both inflammatory markers, leukocyte count and asthma duration as well. Krouse [18] reported that the degree of allergic reactivity is associated with the radiologic appearance of the sinus mucosa on CT scan. However, none of them studied the effect of immunotherapy on the CT scan scoring.

In our study, the recurrence rate in group I patients who were treated with FESS only was 38.9% (7/18), whereas in group III patients who were treated with postsurgical immunotherapy it was 30% (6/20).

Bellussi *et al*. [7] collected data from the studies conducted on NP from 1997 to 2007; they found that the recurrence rate of NP following endoscopic sinus surgery has been widely reported, with varied results ranging from 13 to 75% with a mean of 38.15%, which match with our results.

Although we noticed a decrease in the recurrence rate in group III, there was no statistical significance between the recurrence rate in group I and group III, which may be due to small sample size and limited follow-up duration 'research time limit'. We recommend wide-scale, long-term investigation.

An important finding was that patients who were treated with postsurgical immunotherapy showed a more delay in the onset of recurrence (12–16 months) compared with patients who were treated with FESS alone (7–13 months).

In some protocols of SCIT, the maintenance dose administration is reduced to biweekly and then to monthly intervals for a period of 3–5 years [21]. We suggest that more prolonged courses of SCIT may have significant influence on the recurrence rate. The improvement achieved by SCIT may be attributed to the anti-inflammatory effect of immunotherapy on induced T cell tolerance by several methods, including decreased allergen-induced proliferation, alteration of secreted cytokines, stimulation of apoptosis, and the production of T regulatory cells. This results in a reduction in inflammatory cells and mediators in the affected tissues, the production of blocking antibodies, and the suppression of IgE [22,23].

The final result of our study shows that there was no statistically significant difference between postoperative immunotherapy and FESS alone regarding the CT scores, the nasal endoscopy scores, and the recurrence rate of NP; however, postoperative immunotherapy can provide significant clinical improvement of patients' symptoms, especially sneezing, postnasal discharge, and embarrassment. It can also delay the onset of NP recurrence.

Immunotherapy for atopic patients with NP is considered an adjuvant nonsurgical treatment controlling polyp size and improving patients' symptoms and the quality of life. However, it was not able alone to provide clinical satisfactory improvement for all patients.

Conclusion

In this study, we found that immunotherapy decreases the size of nasal polyps, decreases CT scores, and helps in improving patients' clinical symptoms and subsequently their quality of life; postoperative immunotherapy in addition can delay the recurrence, although it does not decrease the recurrence rate significantly. Large scale studies with longer follow-up results are recommended to elaborate more decisive results.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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