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Clinical Efficacy and Possible Mechanism of Endoscopic Vidian Neurectomy for House Dust Mite-Sensitive Allergic Rhinitis

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Keywords
Allergic rhinitis · Endoscopic vidian neurectomy · Immunoglobulin E · Cytokines · Substance

Abstract
Background/Aims: Endoscopic vidian neurectomy (EVN) for allergic rhinitis (AR) has good clinical effects. However, the pathophysiological basis of the effect of EVN on AR is still poorly understood. This study aimed to investigate the efficacy of EVN on house dust mite (HDM)-sensitive AR and the dynamic changes of serum immunoglobulin E and some immune regulatory factors. ***Methods:*** Twenty HDM-sensitive AR patients were treated with bilateral EVN (EVN group), 15 HDM-sensitive AR patients were treated with subcutaneous immunotherapy (SCIT group), and 15 healthy subjects served as healthy controls. Quality of daily life was assessed by the scores of the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQs). The visual analog scale was used to assess clinical efficacy. Serum molecules were measured by ELISA and the UNICAP system. ***Results:*** Compared with the SCIT group, the RQLQs in the EVN group were lower 12 months after treatment (both $p < 0.05$). There was no significant difference in improving nasal itching and sneezing (both $p > 0.05$), but the clinical efficacy of bilateral EVN was greater than SCIT in improving nasal obstruction, rhinorrhea, eye itching, and lachrymation 12 months after treatment (all $p < 0.05$). Compared with before treatment, the serum levels of total immunoglobulin E (tIgE), *Dermatophagoides pteronyssinus*- and *Dermatophagoides farinae*-specific immunoglobulin E (sIgE), and tumor necrosis factor (TNF)-α in the EVN group and the serum levels of TNF-α and interleukin-4 in the SCIT group were lower 12 months after treatment (all $p < 0.05$). ***Conclusion:*** The short-term efficacy of bilateral EVN is more effective than SCIT in treating HDM-sensitive AR. This may be because the surgery reduced the tIgE and sIgE levels. TNF-α may be involved in the therapeutic mechanism.

Introduction

Allergic rhinitis (AR) is a type I hypersensitivity reaction mediated by immunoglobulin E (IgE) to airborne allergens [1]. In Southern China, the sensitization of AR is mainly monosensitization, and the dominant allergen is house dust mites (HDM) [2]. The clinical characteristics of AR include nasal itching, nasal congestion, sneezing,

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Table 1. Basic clinical characteristics of the patients

	HC group (n = 15)	EVN group (n = 20)	SCIT group (n = 15)	p value
Mean age (SD), years	30.33 (7.92)	31.45 (7.76)	29.33 (8.50)	0.760
Male/female, n	9/6	10/10	10/5	0.603
Positive to Dp (++/+++/++++), n	Negative	5/11/4	3/9/3	0.825
Positive to Df (++/+++/++++), n	Negative	4/11/5	3/8/4	0.943
Mean duration (SD), years		14.60 (1.22)	14.75 (1.16)	0.931

HC, healthy controls; EVN, patients undergoing endoscopic neurotomy; SCIT, patients treated with Dp subcutaneous immunotherapy; Dp, *D. pteronyssinus*; Df, *D. farina*; SD, standard deviation.

and rhinorrhea. AR patients usually also have allergic conjunctivitis [3]. Research suggests that AR has negative impacts on the daily lives of patients, including underperformance at work, poor sleep quality, and cognitive and mood impairment [4].

The clinical treatment of AR mainly includes drug therapy, allergen immunotherapy (AIT), and surgery [5]. Some allergy-relief drugs such as intranasal corticosteroids and antihistamines have been used for years or decades to treat AR but have no long-term effect, and the patient needs repeated medication [6]. Allergen-specific immunotherapy (SIT), including subcutaneous immunotherapy (SCIT), induces immunologic allergen-specific immune tolerance [7]. However, some patients do not respond optimally to SIT [8, 9]. With the rapid development of computed tomography examination technology and endoscopic technology, the localization of the vidian canal has become more accurate, and the vision of endoscopic vidian neurectomy (EVN) clearer [10]. EVN for AR has been found to have good clinical effects [11, 12]. However, the pathophysiological basis of the effect of EVN on AR is still poorly understood.

The purpose of our study was to compare bilateral EVN and SCIT with respect to their clinical effects on HDM-sensitive AR and to analyze the changes in several molecules with key roles in the immune and inflammatory responses. Thus, we quantified the levels of serum total IgE (tIgE), specific IgE (sIgE), T-helper (Th) cell cytokines such as interferon (IFN)-γ and interleukin (IL)-4, tumor necrosis factor (TNF)-α (a pro-inflammatory cytokine), and substance P (SP). We also sought to explore the uniqueness of EVN in improving clinical symptoms and the underlying potential physiological mechanism.

Methods

Study Population

This was a retrospective study. Both serum IgE testing ≥0.7 kAU/L and skin prick test (SPT) ≥ "++" confirmed the allergens. We selected 35 HDM-sensitive moderate to severe persistent AR patients and 15 healthy control subjects from May 13, 2018 to October 31, 2018. These patients not only had serious nasal obstruction, rhinorrhea, nasal itching, and sneezing, but also had different degrees of eye itching and lachrymation. The patients chose their treatment according to their self-selection, among these 20 who were unwilling to undergo immunotherapy had undergone bilateral EVN (EVN group), and 15 had received SCIT (SCIT group). Fifteen healthy subjects served as a healthy control (HC) group. Table 1 shows the characteristics of the subjects. The diagnosis of AR was made according to the clinical symptoms, the examination of nasal mucosa, and the examination of allergens [1]. The exclusion criteria were the following: nasal infection, eye infections, nasal obstruction including septal deviation, nasal polyps, and nasal cavity tumors, as well as severe systemic diseases, including heart disease, hypertension, and diabetes, and also severe immune system problems, including asthma and allergic dermatitis. This study was approved by the Medical Research Ethics Committee of The First Affiliated Hospital of Nanchang University, Nanchang, China.

Skin Prick Test

SPT was performed with standard extracts (ALK-Abelló, Hørsholm, Denmark). A total of 16 aeroallergens including *Dermatophagoides pteronyssinus* (Dp), *Blomia tropicalis*, willow, *Alternaria tenuis*, dog hair, *Artemisia argyi*, *Aspergillus niger*, ragweed, *Humulus lupulus*, cat hair, *Platanus acerifolia*, *Blattella germanica*, *Populus tremula*, *Dermatophagoides farinae* (Df), birch, and *Ulmus pumila*. We used histamine as a positive control. Fifteen minutes after exposure to allergens and histamine, we used a method described previously to evaluate the results of SPT [13].

Treatments

Bilateral EVN

We performed bilateral EVN under endotracheal intubation and general anesthesia. Under direct vision of a wide-angle nasal endoscope, we used pieces of surgical cotton soaked in xylometazoline hydrochloride to shrink the blood vessels of nasal mu-

cosa enough to improve visualization. We used a sickle knife to make an incision at the attachment of the end of the middle turbinate, and then found the sphenopalatine foramen. The anterior opening of the vidian canal was at the posterolateral side of the sphenopalatine foramen [14]. After probing and cutting the vidian nerve with the nerve crochet, the tissue around the opening of the vidian canal was fully coagulated using a plasma knife. The procedure was performed bilaterally.

Dp Subcutaneous Immunotherapy

A standardized treatment plan of conventional SCIT and commercial standardized injections with extract of Dp (Alutard SQ; ALK-Abelló) were performed in the SCIT group as previously described. The first injection volume was 20 SQ-U/mL; over the next 14 weeks the drug was injected once a week, with doses increasing by 20, 40, 80, 200, 400, 800, 2,000, 4,000, 8,000, 10,000, 20,000, 40,000, 60,000, 80,000, and 100,000 SQ-U/mL; the injection interval was then gradually extended to 6 weeks until the end of treatment and the dose was maintained at 100,000 SQ-U/mL [15]. After each injection, we observed the patients for 30 min. We recorded and adverse reactions the patients had after the injection.

Drug Treatment

Depending on the clinical situation of AR after EVN or SCIT treatment, patients received appropriate drugs such as nasal decongestants and antihistamines for emergency treatment.

Quality of Life and Clinical Symptom Evaluation

The patients' quality of daily life was assessed by the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) [16]. The severity of nasal and ocular symptoms was assessed by visual analog scale (VAS) [17], which ranged from 0 (asymptomatic) to 100 (extremely poor). The main evaluation contents of VAS include nasal-specific symptoms of AR and ocular-specific symptoms (eye itching and lachrymation).

Follow-Up Visit

Before treatment, the initial RQLQ and VAS scores were taken from each participant. All the patients in the EVN group were interviewed monthly in the first 6 months and then surveyed every 6 months. At each follow-up, patients completed the RQLQ and VAS scores and self-reported their discomfort. Then we recorded the type and severity of complications. The patients in the SCIT group were followed up at the time of each injection. During each review, RQLQ and VAS scores were completed before injection, and we recorded the type and severity of adverse reactions after the injection. The survey included clinic interviews and internet software interviews.

Clinical Efficacy of Bilateral EVN and SCIT

We compared the clinical efficacy of bilateral EVN and SCIT at 12 months after treatment. VAS was used to test clinical efficacy. The rate of improvement was calculated as: (VAS score prior to treatment – VAS score post-treatment)/VAS score prior to treatment × 100%. The improvement was defined as high if ≥66%, moderate if between 26 and 65%, and not observed if ≤25%. Efficacy was calculated as: number with moderate and high improvement/total number × 100% [15].

Blood Sample Collection

An initial blood sample was taken from all participants on the day in which individuals were enrolled in our study. At 4 and 12 months after treatment, each patient returned to the hospital to provide a 5-mL peripheral blood sample. Before each blood sample collection, any medication with a high risk of anaphylaxis or drug interference was discontinued for drug-specific washout periods. These were 2 days for nasal decongestants in general, 4–5 days for topical antihistamines, 48–72 h for nasal corticosteroids, and 48 h to 1–2 weeks for oral antihistamines (the specific drugs determined the exact interval). Each peripheral venous blood sample was taken by an experienced nurse in an aseptic procedure, and the serum was then immediately isolated by centrifugation (Thermo ST16R) at 3,000 rpm for 10 min. We collected the serum and stored it in sterile conditions at –80 °C for later use.

ELISA and Serum IgE Measurements

The serum IFN-γ, IL-4, TNF-α, SP, and tIgE were measured by ELISA with commercial human IFN-γ, IL-4, TNF-α, SP, and human IgE kit (Elabscience Biotechnology Co. Ltd, Wuhan, China). We used the UNICAP system (Pharmacia, Uppsala, Sweden) to detect the concentration of serum Df and Dp sIgEs. In our study, all the serum samples were anonymized during experimental operations.

Statistical Analysis

For categorical data, χ^2 or Fisher exact tests were performed. We presented continuous variable data as the mean (SD). We used the Student *t* test or Mann-Whitney U test to compare the evaluation for intergroup comparisons. One-way ANOVA or non-parametric test was used for the evaluation before and after treatment and among the 3 groups. p values <0.05 were considered statistically significant. We performed the statistical analysis with SPSS statistical software version 22.0.

Results

Changes in RQLQ Scores

Compared with the baseline scores, the scores of RQLQs were significantly decreased at 4 months after treatment in the EVN group ($p < 0.001$; Fig. 1a) and SCIT group ($p < 0.001$; Fig. 1b). However, there was no intergroup difference at 4 months after treatment ($p > 0.05$; Fig. 1c). Compared with the data at 4 months, both the RQLQs in the EVN group and SCIT group showed no further decline at 12 months after treatment (for both $p > 0.05$; Fig. 1a, b). However, at 12 months after treatment, the RQLQs of the EVN group were lower compared with the SCIT group ($p < 0.01$; Fig. 1c). The daily life of the HC group was not affected (Fig. 1c). This finding showed that both bilateral EVN and SCIT can improve the AR patients' quality of daily life. Interestingly, bilateral EVN was more effective than SCIT at 12 months after treatment.

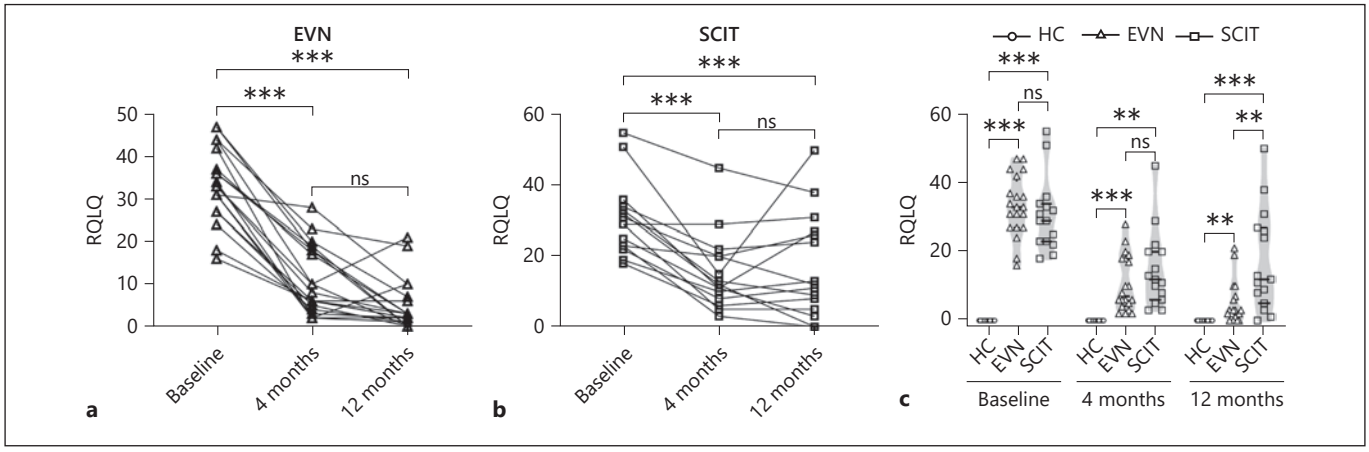

Fig. 1. Changes in quality of daily life after treatments. RQLQ was evaluated in the EVN, SCIT, and HC groups. **a**, **b** Data are shown as line charts with individual values. **c** Data are shown as violin plots with individual values and data distributions. ** $p < 0.01$, *** $p < 0.001$. HC, healthy control subjects ($n = 15$); EVN, patients undergoing bilateral endoscopic neurotomy ($n = 20$); SCIT, patients treated with Dp subcutaneous immunotherapy ($n = 15$); baseline, before treatment; 4 months, 4 months after treatment; 12 months, 12 months after treatment; ns, not significant.

Clinical Efficacy

Compared with the baseline scores, the VAS values of nasal obstruction (Fig. 2a), rhinorrhea (Fig. 2b), nasal itching (Fig. 2c), sneezing (Fig. 2d), eye itching (Fig. 2e), lachrymation (Fig. 2f), and total symptoms (Fig. 2g) were decreased at 4 months after treatment in the EVN group (all $p < 0.05$). However, these symptom scores in the EVN group at 12 months after treatment were not significantly different from the data at 4 months after surgery (all $p > 0.05$; Fig. 2a, g). In the SCIT group, compared with the baseline scores, VAS values of nasal obstruction (Fig. 2a), rhinorrhea (Fig. 2b), nasal itching (Fig. 2c), and total symptoms (Fig. 2g) declined significantly at 4 months after treatment. However, the VAS results for sneezing (Fig. 2d), eye itching (Fig. 2e), and lachrymation (Fig. 2f) showed no significant decline at 4 months after treatment. Compared with the baseline scores, VAS values for nasal obstruction (Fig. 2a), nasal itching (Fig. 2c), sneezing (Fig. 2d), lachrymation (Fig. 2f), and total symptoms (Fig. 2g) in the SCIT group declined significantly at 12 months after treatment. However, the VAS results for rhinorrhea (Fig. 2b) and eye itching (Fig. 2e) showed no significant decline at 12 months after treatment (both $p > 0.05$). Bilateral EVN showed a higher clinical efficacy than SCIT in improving nasal obstruction, rhinorrhea, eye itching, lachrymation, and total symptoms scores (all $p < 0.05$; Fig. 2h). We found no difference between bilateral EVN and SCIT in improving nasal itching and sneezing at 12 months after treatment (all $p > 0.05$; Fig. 2h).

Effects of Bilateral EVN and SCIT on the Levels of Serum IgE

Compared with the preoperative baseline, serum tIgE (Fig. 3a), Dp sIgE (Fig. 3b), and Df sIgE (Fig. 3c) levels decreased at 12 months after treatment in the EVN group (all $p < 0.05$). However, there was no significant difference in serum total IgE (Fig. 3a), Dp sIgE (Fig. 3b), and Df sIgE (Fig. 3c) levels at 4 and 12 months after treatment compared with baseline in the SCIT group (all, $p > 0.05$). The serum total IgE, Dp, and Df sIgE levels between the EVN and SCIT groups all showed no difference at all time points observed (all $p > 0.05$; Fig. 3d, f).

Changes of Serum IFN-γ, IL-4, TNF-α, and SP

The serum IFN-γ levels in the EVN and SCIT groups before treatment were lower than in the HC group (both $p < 0.05$; Fig. 4a). However, compared with baseline, there was no significant change in serum IFN-γ at 4 and 12 months after treatment both in the EVN and SCIT groups (both $p > 0.05$; Fig. 4a). Compared with the baseline, both the serum IL-4 (Fig. 4b) and TNF-α levels (Fig. 4c) decreased at 4 and 12 months after treatment in the SCIT group (all $p < 0.05$). The initial levels of serum IL-4 (Fig. 4d) and TNF-α (Fig. 4e) in the EVN and SCIT groups were higher than in the HC group (all $p < 0.05$). The serum IL-4 (Fig. 4d) in the SCIT group returned to normal levels as of 12 months after treatment, and TNF-α (Fig. 4e) levels in the SCIT group declined to normal levels at 4 months after treatment. However, in the EVN group,

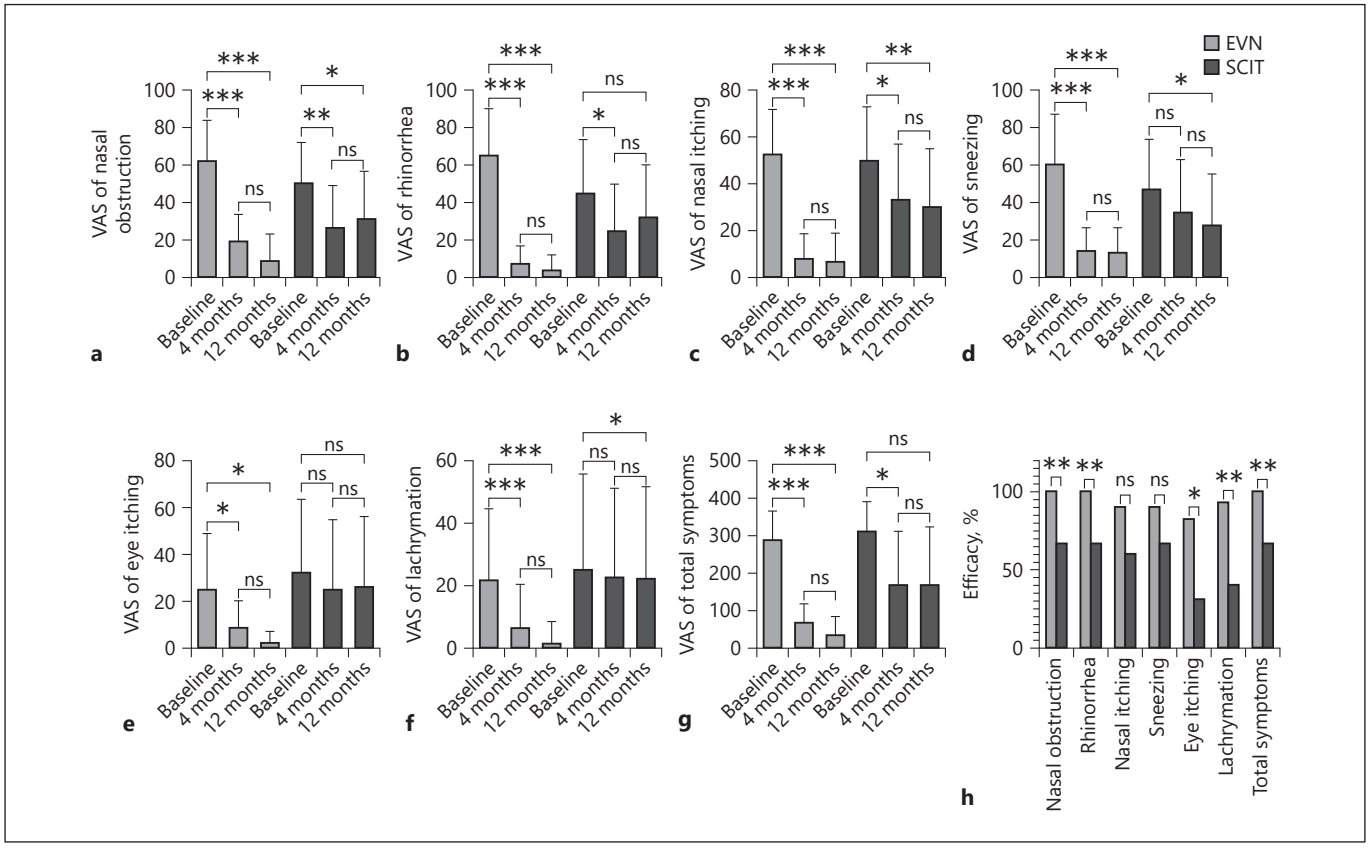

Fig. 2. Efficacy rate between bilateral EVN and SCIT for AR. VAS of nasal obstruction (**a**), rhinorrhea (**b**), nasal itching (**c**), sneezing (**d**), eye itching (**e**), lachrymation (**f**), and total symptoms (**g**) were evaluated in the EVN group and SCIT group. h The efficacy for these symptoms was compared separately between the EVN group and SCIT group at 12 months after treatment. Data are shown as bar charts for individual parameters. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. HC, healthy control subjects ($n = 15$); EVN, patients undergoing bilateral endoscopic neurotomy ($n = 20$); SCIT, patients treated with Dp subcutaneous immunotherapy ($n = 15$); baseline, before treatment; 4 months, 4 months after treatment; 12 months, 12 months after treatment; ns, not significant.

only the serum TNF-α level decreased to normal levels at 12 months after treatment ($p < 0.05$; Fig. 4e); notably, serum IL-4 did not change at 12 months after surgery, although it showed a downward trend ($p > 0.05$; Fig. 4b). For at least 1 year of follow-up, there was no significant difference in the serum IL-4 and TNF-α levels between the EVN and SCIT groups (all $p > 0.05$; Fig. 4d, f). No significant difference was shown in the serum SP among the 3 groups before treatment, and no significant change was found in serum SP before or after treatment in either the EVN group or the SCIT group (all $p > 0.05$; Fig. 4f).

Complications and Adverse Reactions

In our study, 4 patients (20%) reported mild dry eye and mild eye strain after surgery, which resolved after 1–3 months with or without eye drops, and our patients had no other ophthalmological problems, such as vision loss or eye movement disorder. Two patients (10%) in the EVN group reported numbness in the upper lip/palate during their follow-up, and in 1 of these patients this symptom disappeared within 6 months with the use of vitamin B. Another patient had unilateral upper lip/mouthfeel numbness symptoms that lasted for almost a year. We did not observe other severe complications, including intraoperative or massive bleeding during the operation, or trauma of the oculomotor nerve. During the 1 year of SCIT in the present study, local reactions (LRs) of SCIT occurred in 71 (21.5%) of the total 330 subcutaneous injections. One patient experienced mild chest tightness following an injection therapy, which was quickly relieved by the emergency inhalation of albuterol. No other systemic reactions (SRs) occurred in our study.

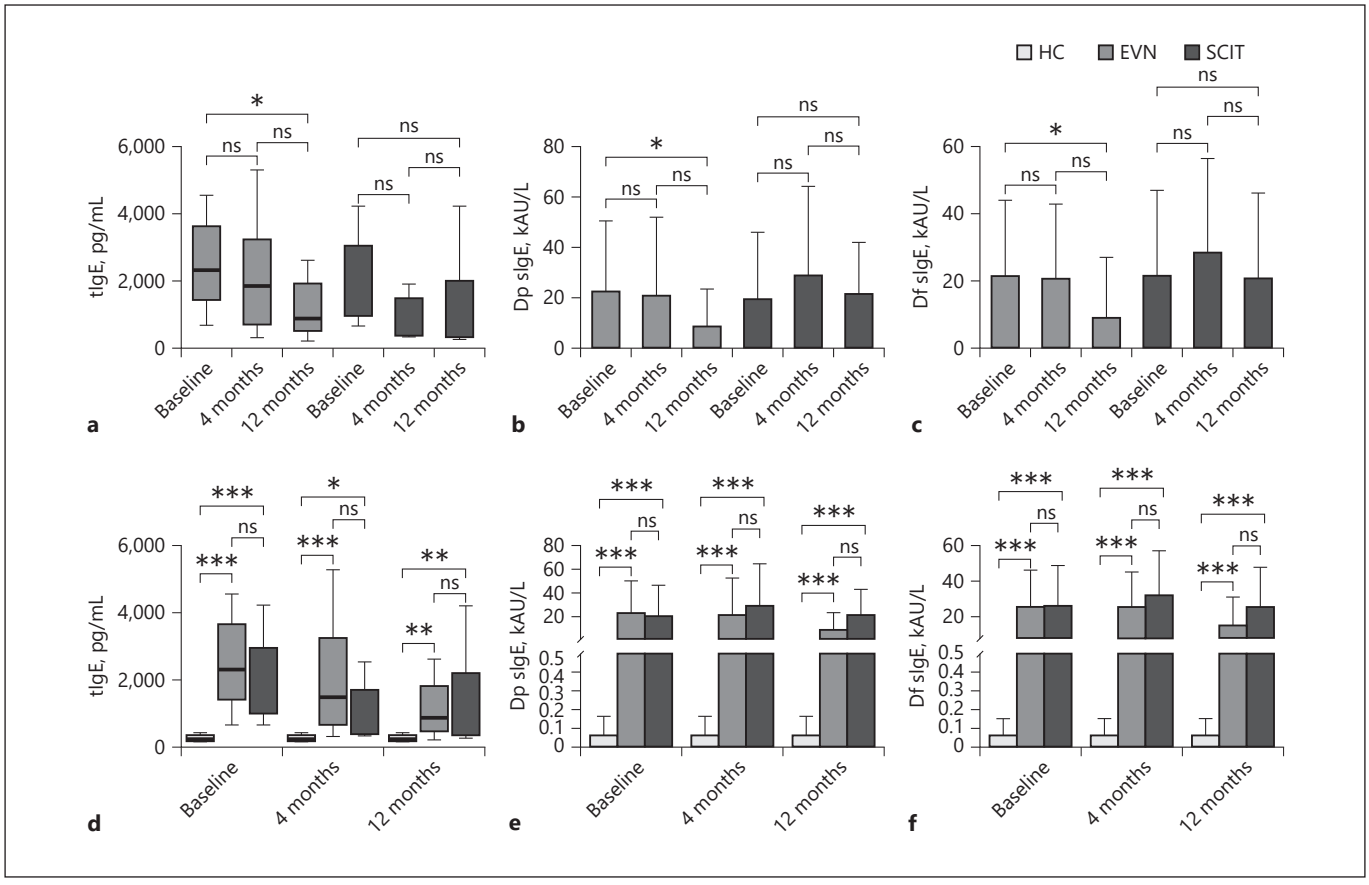

Fig. 3. Changes in serum tIgE and sIgE. Serum tIgE (**a**), Dp sIgE (**b**), and Df sIgE (**c**) levels of AR patients were compared before and after bilateral EVN or SCIT treatment, respectively. Serum tIgE (**d**), Dp sIgE (**e**), and Df sIgE (**f**) levels were compared among the HC, EVN, and SCIT groups. Data are shown as bar charts for individual parameters. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. HC, healthy control subjects ($n = 15$); EVN, patients undergoing bilateral endoscopic neurotomy ($n = 20$); SCIT, patients treated with Dp subcutaneous immunotherapy ($n = 15$); baseline, before treatment; 4 months, 4 months after treatment; 12 months, 12 months after treatment; ns, not significant.

Discussion

We conducted a separate longitudinal comparison of 2 different treatments for AR. We found that both bilateral EVN and SCIT enhanced the patient's quality of life and improved their clinical symptoms, which were observations consistent with other studies [15, 18]. Interestingly though, we were the first to conduct a comparative study on bilateral EVN and SCIT in the treatment of AR. We discovered that bilateral EVN was more effective than SCIT in improving the quality of daily life and the symptoms of nasal obstruction, rhinorrhea, eye itching, and lachrymation at 12 months after treatment. Our data also showed that bilateral EVN and SCIT have the same clinical effect for nasal itching and sneezing at 12 months after treatment. Also, bilateral EVN reduced the level of serum tIgE, sIgE, and TNF-α in AR patients at 12 months after surgery.

SCIT has been proven to have a good long-term clinical effect on AR. Jacobsen et al. [19] established that a 3-year course of SCIT offers a sustained clinical benefit for up to 7 years after discontinuation. Ai et al. [18] reported that 3 years after bilateral EVN treatment for AR the clinical efficacy of surgery is still good. Our data suggested that EVN treatment is better than SCIT at 1 year after treatment. However, considering that the patients in the SCIT group had been receiving immunotherapy for only 1 year, immunotherapy did not achieve its maximum effectiveness within the period of the study [20]. Thus, we need a longer follow-up to confirm whether the

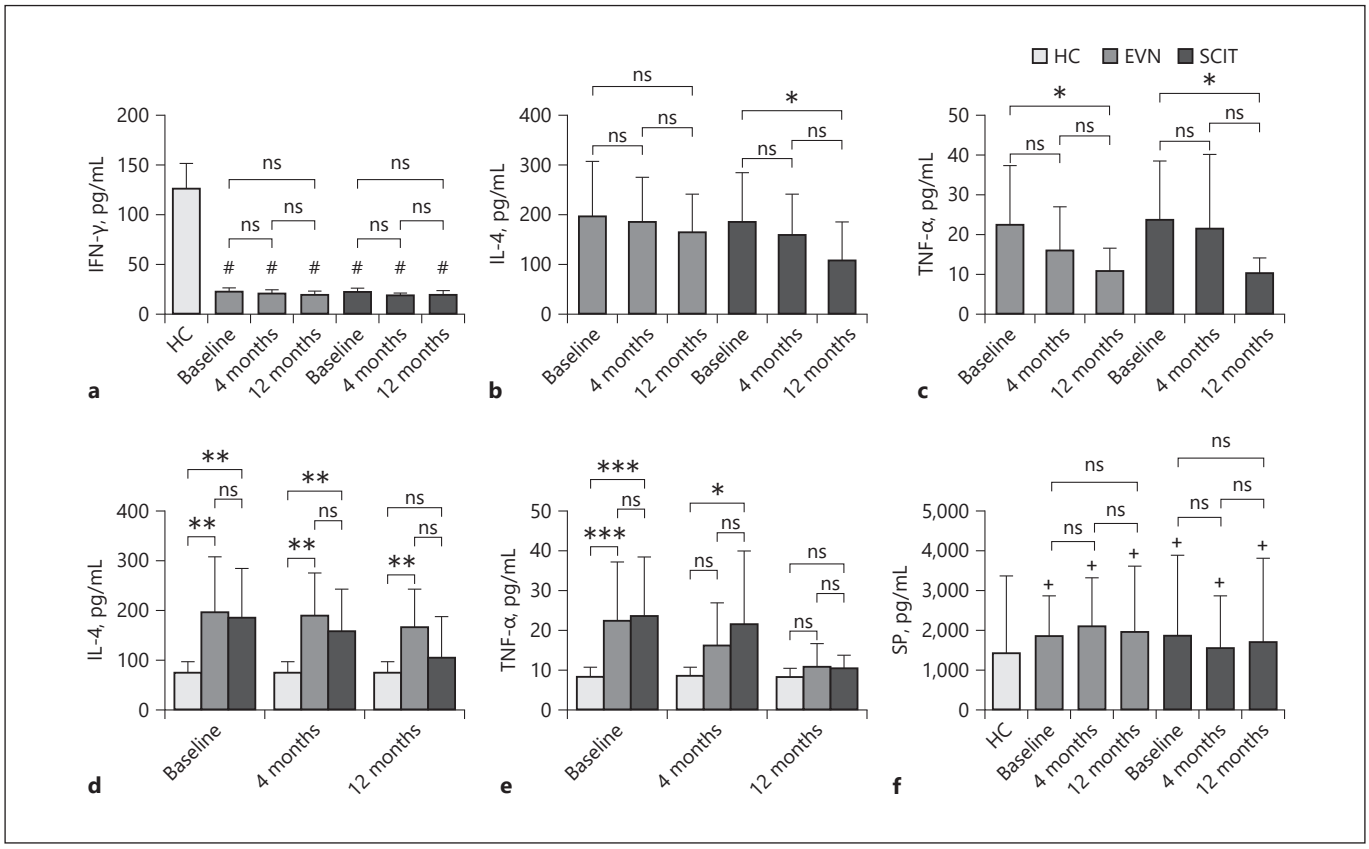

Fig. 4. Changes in serum IFN-γ, IL-4, TNF-α, and SP. **a** Serum IFN-γ measured in the HC, EVN, and SCIT groups. Serum IL-4 (**b**) and TNF-α (**c**) levels of AR patients were compared before and after bilateral EVN or SCIT treatment, respectively. Serum IL-4 (**d**) and TNF-α (**e**) levels were compared among the HC, EVN, and SCIT groups. **f** Serum SP was measured in the HC, EVN, and SCIT groups. Data are shown as bar charts for individual data. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$; # $p < 0.05$ compared with the HC group; + $p > 0.05$ compared with the HC group. HC, healthy control subjects ($n = 15$); EVN, patients undergoing bilateral endoscopic neurotomy ($n = 20$); SCIT, patients treated with Dp subcutaneous immunotherapy ($n = 15$); baseline, before treatment; 4 months, 4 months after treatment; 12 months, 12 months after treatment; ns, not significant.

clinical efficacy of bilateral EVN is better than that of a long and continuous SCIT treatment.

An EAACI position paper [9] pointed out that the tIgE and sIgE levels during AIT vary from study to study. Whether it remained unchanged, increased, or decreased seems to depend largely on the sampling time, but the sIgE levels have been proven to eventually decline over time. Our data showed that there were no significant changes in the serum tIgE, Dp sIgE, and Df sIgE levels in the SCIT group at 4 and 12 months after treatment. However, it is interesting to note that bilateral EVN reduced the levels of peripheral serum tIgE, Dp sIgE, and Df sIgE of the AR patients at 12 months after surgery, which has not been reported before. Studies on EVN have focused on clinical efficacy and the selection of surgical methods [11, 14, 18]. The vidian nerve comprises parasympathetic fibers (main composition) and sympathetic fibers. Parasympathetic fibers dominate both the vasodilatation and the exocrine glands of the nasal mucosa, and the sympathetic nervous system predominates and maintains vascular tension [21, 22]. In a pathological condition, the release of neuropeptides and acetylcholine in nasal mucosa innervate vasorelaxation and increases nasal obstruction and secretion [23]. Vidian neurectomy could cause vasoconstriction of the nasal mucosa and decreased glandular secretion [24]. After surgery and within the 12 months of follow-up in our study, we also observed a significant improvement of the pallor and edema of the nasal mucosa of AR patients. Therefore, we hypothesize that the possible mechanism for the serum tIgE and sIgE decrease

after surgery is related to the bilateral EVN alleviation of the nasal mucosa inflammatory response in the AR patients.

The increased tendency to apoptosis of activated Th1 cells might account for the predominant response of Th2 cells in allergic diseases [25]. Consistent with the literature [26], in our study, the levels of serum IFN-γ and IL-4 in the AR patients were lower and higher than in the HC group, respectively. In addition to avoiding allergens, SIT is currently the only immunity-modifying treatment for allergens, it induces a return to normal balance between Th2 and Th1 [27, 28]. Unfortunately, in the present study, neither bilateral EVN nor SCIT increased the serum IFN-γ levels of the AR patients within 1 year after treatment. AIT is also expected to downregulate the inflammatory cytokines and chemokines [29, 30]. Our data showed that SCIT could reduce IL-4 and TNF-α levels in the peripheral blood, and these players may participate in the intrinsic mechanism of immunotherapy for AR. Intriguingly, we found that bilateral EVN also reduced the serum TNF-α of AR patients at 12 months after surgery. Studies have shown that TNF-α is involved in type I hypersensitivity reactions as a pro-inflammatory cytokine. TNF-α is released during allergic responses from both mast cells and macrophages through IgE-dependent mechanisms by enhancing the effect of IL-4 [31, 32]. TNF-α is necessary for raising Th2 and eosinophils cells to the site of allergic inflammation, and also required for the production of Th2-type cytokines [31, 33]. In our study, serum TNF-α decreased and serum IL-4 showed a declining trend after surgery. Based on some previous studies, inhibition of cholinergic nerve hyperactivity using ipratropium bromide decreased expression of IL-4 mRNA in the nasal mucosa of BALB/c mice [34], and in vitro cholinergic nerve inhibition with ipratropium bromide decreased AR CD4 T cell polarization into Th2 cells partially through an Akt-dependent mechanism [35]. All these findings showed that inhibition of cholinergic nerve hyperactivity by cutting off the bilateral vidian nerve could change the inflammatory state of AR. IL-4 and TNF-α may play an important intermediate role; however, the underlying mechanism still needs to be explained.

Parasympathetic fibers release acetylcholine and neuropeptide transmitters, such as SP and nerve growth factor [23]. Chalastras et al. [36] found that the increases of some neuropeptides, including SP in the nasal mucosa, were correlated with symptoms of AR. Ma et al. [37] reported that bilateral EVN reduced the levels of SP in the nasal mucosa. Since it was difficult to get postoperative nasal mucosa specimens from our patients, we tried to monitor the changes of SP in the peripheral blood in our study. However, our data indicated that serum SP cannot be used as a readout of the neuroimmune status of the nasal mucosa.

The complications and adverse reactions should not be ignored. The most common postoperative complications of EVN are eye dryness and numbness in the upper lip/palate [18, 37]. Although there were no serious postoperative complications in our study, 4 (20%) patients in the EVN group reported mild eye dryness and mild eye strain, and 2 (10%) reported numbness in the upper lip/palate after surgery. Fortunately, and consistently with previous reports [18], within 1 year after surgery the patients had recovered from these complications. Furthermore, as mentioned there were no other ophthalmological problems. We should state that most of these complications occurred in the early stage of our study, and the incidence of surgical complications decreased with the accumulation of surgical experience and the strengthening of the intraoperative protection of the surrounding structures of the vidian canal. For SCIT, LRs are defined as pruritus and/or erythema at the site of injection. Immediate erythema with a diameter >5 cm and tardive erythema with a diameter >10 cm were defined as LRs. The SRs included nettle rash, dyspnea, angioedema, and allergic shock. James and Bernstein [38] showed that the rates of LRs and SRs of SCIT were 26–86% and 0.1–0.2%, respectively. During the 1 year of SCIT in our experiment, the incidence rates of LRs and LRs to SCIT treatment were 21.5 and 0.3%, respectively.

Patients with refractory AR who choose SCIT need to go back and forth to the hospital for treatment repeatedly. The time and economic costs are high, and the therapeutic effect for some patients is still not ideal. Thus, we consider that bilateral EVN is a good choice for adult patients with refractory AR for whom immunotherapy has failed or who are not expected to adhere to regular immunotherapy and are eager to improve their condition.

Conclusions

Considering a 12-month follow-up period, our results showed that bilateral EVN is more effective than SCIT in treating HDM-sensitive AR. This may be because the surgery reduced tIgE and sIgE levels. At the same time, TNF-α may be involved in the therapeutic mechanism. However, the follow-up time of our study was relatively short, and the different long-term effects of EVN and SCIT require further investigation.

Statement of Ethics

This research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki and was approved by the Medical Research Ethics Committee of The First Affiliated Hospital of Nanchang University, Nanchang, China (2019 Medical Research Review No. 027). Each of the participants in this study signed an informed consent form.

Conflict of Interest Statement

All authors report no conflicts of interest and no financial relationships with relevant commercial interests.

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Author Contributions

L.S. and J.Y. contributed to the conception of the study. J.W., M.L., M.H., and J.T. helped to follow-up and collect the specimens. L.S. and Z.H. contributed significantly to analysis of the data. L.S., X.K., and L.L. wrote the manuscript.

References

1 Brożek JL, Bousquet J, Agache I, Agarwal A, Bachert C, Bosnic-Anticevich S, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines – 2016 revision. J Allergy Clin Immunol. 2017 Oct;140(4):950–8.

2 Tao XY, Ng CL, Chen D, Lin ZB, Wu SL, Liang MJ, et al. Clinical characteristics and allergen sensitization patterns of patients with local allergic rhinitis in Southern China. Int Arch Allergy Immunol. 2018;175(1-2):107–13.

3 Roberts G, Pfaar O, Akdis CA, Ansotegui IJ, Durham SR, Gerth van Wijk R, et al. EAACI Guidelines on Allergen Immunotherapy: allergic rhinoconjunctivitis. Allergy. 2018 Apr;73(4):765–98.

4 Zhang Y, Zhang L. Increasing Prevalence of Allergic Rhinitis in China. Allergy Asthma Immunol Res. 2019 Mar;11(2):156–69.

5 Subspecialty Group of Rhinology, Editorial Board of Chinese Journal of Otorhinolaryngology Head and Neck Surgery; Subspecialty Group of Rhinology, Society of Otorhinolaryngology Head and Neck Surgery, Chinese Medical Association. Chinese guidelines for diagnosis and treatment of allergic rhinitis. Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2016 Jan;51(1):6–24.

6 Meltzer EO, Blaiss MS, Naclerio RM, Stoloff SW, Derebery MJ, Nelson HS, et al. Burden of allergic rhinitis: allergies in America, Latin America, and Asia-Pacific adult surveys. Allergy Asthma Proc. 2012 Sep-Oct;33(5 Suppl 1):S113–41.

7 Möbs C, Ipsen H, Mayer L, Slotosch C, Petersen A, Würtzen PA, et al. Birch pollen immunotherapy results in long-term loss of Bet v 1-specific TH2 responses, transient TR1 activation, and synthesis of IgE-blocking antibodies. J Allergy Clin Immunol. 2012 Nov;130(5):1108–1116.e6.

8 Shamji MH, Durham SR. Mechanisms of allergen immunotherapy for inhaled allergens and predictive biomarkers. J Allergy Clin Immunol. 2017 Dec;140(6):1485–98.

9 Shamji MH, Kappen JH, Akdis M, Jensen-Jarolim E, Knol EF, Kleine-Tebbe J, et al. Biomarkers for monitoring clinical efficacy of allergen immunotherapy for allergic rhinoconjunctivitis and allergic asthma: an EAACI Position Paper. Allergy. 2017 Aug;72(8):1156–73.

10 Lee JC, Kao CH, Hsu CH, Lin YS. Endoscopic transsphenoidal vidian neurectomy. Eur Arch Otorhinolaryngol. 2011 Jun;268(6):851–6.

11 Zhang H, Micomonaco DC, Dziegielewski PT, Sowerby LJ, Weis E, Wright ED. Endoscopic vidian neurectomy: a prospective case series. Int Forum Allergy Rhinol. 2015 May;5(5):423–30.

12 Zhao C, Ji Y, An Y, Xue J, Li Q, Suo L, et al. An Alternative Method of Endoscopic Intrasphenoidal Vidian Neurectomy. OTO Open. 2018 Mar 13;2(1):2473974X18764862.

13 Haahtela T, Burbach GJ, Bachert C, Bindslev-Jensen C, Bonini S, Bousquet J, et al. Clinical relevance is associated with allergen-specific wheal size in skin prick testing. Clin Exp Allergy. 2014 Mar;44(3):407–16.

14 Tan G, Ma Y, Li H, Li W, Wang J. Long-term results of bilateral endoscopic vidian neurectomy in the management of moderate to severe persistent allergic rhinitis. Arch Otolaryngol Head Neck Surg. 2012 May;138(5):492–7.

15 Editorial Committee of Chinese Journal of Otorhinolaryngology Head Neck Surgery; Chinese Otorhinolaryngology Society of Chinese Medical Association. Principles of diagnosis and treatment of allergic rhinitis (2004, Lanzhou). Zhonghua Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2005;40(3):166–7.

16 Romano M, James S, Farrington E, Perry R, Elliott L. The impact of perennial allergic rhinitis with/without allergic asthma on sleep, work and activity level. Allergy Asthma Clin Immunol. 2019 Dec;15(1):81.

17 Bousquet PJ, Combescure C, Neukirch F, Klossek JM, Méchin H, Daures JP, et al. Visual analog scales can assess the severity of rhinitis graded according to ARIA guidelines. Allergy. 2007 Apr;62(4):367–72.

18 Ai J, Xie Z, Qing X, Li W, Liu H, Wang T, et al. Clinical effect of endoscopic vidian neurectomy on bronchial asthma outcomes in patients with coexisting refractory allergic rhinitis and asthma. Am J Rhinol Allergy. 2018 May;32(3):139–46.

19 Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Høst A, et al.; The PAT investigator group. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy. 2007 Aug;62(8):943–8.

20 Oktemer T, Altintoprak N, Muluk NB, Senturk M, Kar M, Bafaqeeh SA, et al. Clinical efficacy of immunotherapy in allergic rhinitis. Am J Rhinol Allergy. 2016 Sep;30(5):4–7.

21 Van Gerven L, Steelant B, Hellings PW. Nasal hyperreactivity in rhinitis: A diagnostic and therapeutic challenge. Allergy. 2018 Sep;73(9):1784–91.

22 Nturibi E, Bordoni B. Anatomy, Head and Neck, Greater Petrosal Nerve. StatPearls. Treasure Island (FL): StatPearls Publishing StatPearls Publishing LLC; 2020.

23 Baraniuk JN, Merck SJ. Neuroregulation of human nasal mucosa. Ann N Y Acad Sci. 2009 Jul;1170(1):604–9.

24 Konno A. Historical, pathophysiological, and therapeutic aspects of vidian neurectomy. Curr Allergy Asthma Rep. 2010 Mar;10(2):105–12.

25 Akkoc T, de Koning PJ, Rückert B, Barlan I, Akdis M, Akdis CA. Increased activation-induced cell death of high IFN-gamma-producing T(H)1 cells as a mechanism of T(H)2 predominance in atopic diseases. J Allergy Clin Immunol. 2008 Mar;121(3):652–658.e1.

26 Scadding G. Cytokine profiles in allergic rhinitis. Curr Allergy Asthma Rep. 2014 May;14(5):435.

27 Fujita H, Soyka MB, Akdis M, Akdis CA. Mechanisms of allergen-specific immunotherapy. Clin Transl Allergy. 2012 Jan;2(1):2.
28 Klimek L, Pfaar O, Bousquet J, Senti G, Kündig T. Allergen immunotherapy in allergic rhinitis: current use and future trends. Expert Rev Clin Immunol. 2017 Sep;13(9):897–906.
29 Akdis CA, Akdis M. Mechanisms of allergen-specific immunotherapy and immune tolerance to allergens. World Allergy Organ J. 2015 May;8(1):17.
30 Sousa L, Martín-Sierra C, Pereira C, Loureiro G, Tavares B, Pedreiro S, et al. Subcutaneous immunotherapy induces alterations in monocytes and dendritic cells homeostasis in allergic rhinitis patients. Allergy Asthma Clin Immunol. 2018 Nov;14(1):45.
31 Iwasaki M, Saito K, Takemura M, Sekikawa K, Fujii H, Yamada Y, et al. TNF-alpha contributes to the development of allergic rhinitis in mice. J Allergy Clin Immunol. 2003 Jul;112(1):134–40.
32 Eguiluz-Gracia I, Mathioudakis AG, Bartel S, Vijverberg SJ, Fuertes E, Comberiati P, et al. The need for clean air: the way air pollution and climate change affect allergic rhinitis and asthma. Allergy. 2020 Sep;75(9):2170–84.
33 Ahmad S, Azid NA, Boer JC, Lim J, Chen X, Plebanski M, et al. The Key Role of TNF-TNFR2 Interactions in the Modulation of Allergic Inflammation: A Review. Front Immunol. 2018 Nov;9:2572.
34 Hou M, Li W, Xie Z, Ai J, Sun B, Tan G. Effects of anticholinergic agent on miRNA profiles and transcriptomes in a murine model of allergic rhinitis. Mol Med Rep. 2017 Nov;16(5):6558–69.
35 Liu H, Wang T, Xia J, Ai J, Li W, Song Y, et al. Cholinergic neuron-like D-U87 cells promote polarization of allergic rhinitis T-helper 2 cells. Int Forum Allergy Rhinol. 2020 Feb;10(2):233–42.
36 Chalastras T, Nicolopoulou-Stamati P, Patsouris E, Eleftheriadou A, Kandiloros D, Yiotakis I, et al. Expression of substance P, vasoactive intestinal peptide and heat shock protein 70 in nasal mucosal smears of patients with allergic rhinitis: investigation using a liquid-based method. J Laryngol Otol. 2008 Jul;122(7):700–6.
37 Ma Y, Tan G, Zhao Z, Li W, Huang L, Liu G. Therapeutic effectiveness of endoscopic vidian neurectomy for the treatment of vasomotor rhinitis. Acta Otolaryngol. 2014 Mar;134(3):260–7.
38 James C, Bernstein DI. Allergen immunotherapy: an updated review of safety. Curr Opin Allergy Clin Immunol. 2017 Feb;17(1):55–9.