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Effect of Postoperative Specific Immunotherapy Combined with Nasal Irrigation on Chronic Rhinosinusitis with Allergic Rhinitis

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ABSTRACT

Patients with chronic rhinosinusitis (CRS) and allergic rhinitis (AR) (CRSwAR) have a more severe condition with a higher rate of recurrence after endoscopic sinus surgery (ESS). This study aimed to explore the effect of specific subcutaneous immunotherapy (SCIT) and nasal irrigation on CRSwAR after ESS.

Sixty-four patients who were diagnosed as CRSwAR and received ESS were enrolled and divided into groups A, B, and C to receive different postoperative treatment strategies (conventional medication, medication with nasal irrigation, and medication with nasal irrigation and SCIT), and their prognosis was evaluated by scoring, electron microscopy, and inflammatory factors.

One year after ESS, the recurrence rate of group C was significantly reduced; and the scoring from baseline was significantly different among the three groups, which of group C were the best. The epithelium arrangement, cilia morphology, and inflammation of nasal mucosa in each group were better than those in the preoperative state; and those in group C were the best. After one year, the expression levels of eosinophil cationic protein (ECP), interleukin (IL)-8, and IL-17 in group B were lower than those of group A; and the expression levels of ECP, IL-8, IL-25, IL-33, IL-17 in group C were lower than those in group A.

SCIT combined with nasal irrigation can improve the patients' symptoms and quality of life, promote the epithelialization of the mucosa in the surgical cavity, regulate the local immune response of the nasal cavity; thus improve the prognosis of patients with ESS after 1 year.

Keywords: Allergic rhinitis; Immunotherapy; Nasal irrigation

INTRODUCTION

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease of nasal and sinus mucosa, affecting approximately 12.5% of the world's population.[1] In the past decade, with the rapid development of endoscopic surgery and the application of new local and systemic anti-inflammatory drugs, the diagnosis and treatment level of CRS has been greatly improved. However, studies have shown that 19% of CRS patients have to undergo surgery again due to relapse symptoms within 5 years after endoscopic surgery,[2] and 35% of CRS

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patients relapse within 2 months after the end of drug treatment.[3] CRS patients are not only deeply troubled by it, causing certain psychological pressure, but also suffering a heavy financial burden. In addition, a large number of clinical studies have confirmed that patients with both CRS and allergic diseases such as asthma have more severe CRS conditions,[4,5] and the postoperative recurrence rate of endoscopic sinus surgery (ESS) is higher.[6]Early studies have shown that nasal polyposis with allergic constitution involves a wider range of lesions and serious disease changes. Compared with CRS without the allergic disease, T helper (Th) 17/regulatory T cell (Treg) imbalance of CRS with allergic disease is more serious, pathological changes are more serious, such as eosinophil infiltration, thickening of the basement membrane.[7,8] Cao's research on the CRS immune pathological characteristics in China found that both chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP) are the Th1/Th2/Th17mixed response accompanied by Treg dysfunction; the Th1 response is dominant in CRSsNP, while the Th2 response is only found in eosinophilic CRSwNP.[9] Chinese scholar Zhang and Belgian scholar Bachert compared the characteristics of CRSwNP in southern China and Belgium, indicating that Th2 type cytokines are the main component of CRSwNP patients in Belgium, while Th1 and Th17 may be more dominant in polyps samples from Chinese CRSwNP patients.[10] Both CRS and AR have local immune response imbalance and inflammatory response in the nasal cavity, which may be used as targets for cooperative treatment?

At present, specific immunotherapy (SIT) is the only effective way to change the natural processes of allergic diseases through immunomodulatory mechanisms. ARIA2008[11] pointed out that to change the long-term natural course of allergic diseases, specific immunotherapy should be initiated at the beginning of the disease, without the premise of failure of drug treatment, and its application can be more active. Nasal irrigation (NI) is a common method for treating nasal and sinus diseases and has been widely used in the clinic. The saline solution often used for nasal irrigation is hypertonic. It can not only effectively clean the nasal cavity, avoid inhalation of allergens to stimulate the nasal mucosa, but also adjust the humidity and pH of the nose to restore the normal physiological environment. Recent studies have found that nasal irrigation can significantly reduce the concentration of histamine and leukotrienes in the nasal cavity of patients with rhinitis, reduce the chemotaxis of eosinophils and neutrophils, and significantly reduce inflammatory mediators (such as interleukin (IL)-8, RANTES)[12].

In summary, we speculate that SCIT may affect the natural process of allergic airway disease through immune modulation, thereby interfering with the tissue remodeling of CRS mucosa in CRS patients with AR after ESS, which plays an important role in postoperative outcome. Nasal irrigation may also play a role in the immune regulation of the nasal mucosa, inhibit the development of chronic inflammation, and play a synergistic role in the treatment of airway inflammatory diseases, in addition to physical flushing. It is worth studying that what roles do they play and how to play.

MATERIALS AND METHODS

This prospective study was conducted between Aug 2018 and Nov 2019. Sixty-four patients who were diagnosed as CRSwNP with AR and underwent ESS were enrolled. This study has been approved by the Ethics Committee of the First Affiliated Hospital of Chongqing Medical University (Approval number: 201810802).

Inclusion Criteria

According to the diagnostic criteria of EPOS2012[13] and ARIA2008,[11] 64 cases were diagnosed as CRSwNP with AR (2-3 allergens including dust mites) from August 2018 to November 2019 in The First Affiliated Hospital of Chongqing, patients undergoing standardized perioperative management and ESS will be included in the study after obtaining their informed consent.

Exclusion Criteria

Cases with fungal allergic rhinosinusitis or acute rhinosinusitis, sinus tumor, previous immunotherapy within the past 2 years, serious systemic infection, previous immuno-deficiency disease, or medical immunosuppression were excluded.

Group and Interventions

Group A (control group): Normative medication. Group B (medication + nasal irrigation): Normative

drug therapy with physiological seawater nasal irrigation.

Group C (medication + nasal irrigation + specific immunotherapy): Normative drug therapy with physiological seawater nasal irrigation and SCIT.

All the included patients were routinely examined by preoperative sinus CT, nasal endoscopy, and allergen skin prick test (SPT). All patients were advised to receive prescriptive medication and nasal irrigation. Specific subcutaneous immunotherapy was given in patients who showed positive results with 2-3 allergens including dust mites. Those who did not perform or did not adhere to nasal irrigation for 6 months were classified as group A.

Postoperative normative medication: Intranasal glucocorticoids, macrolides, mucus stimulants, antihistamines, and anti-leukotriene for 12 weeks.

Nasal irrigation: Nasal Care (China, Taide). According to the drug instructions, nasal irrigation is performed twice a day for 6 months.

SCIT: Patients received SCIT, Alutard (Denmark, ALK). The course of SCIT is divided into two stages, namely the initial stage and the maintenance stage. The dose and concentration were gradually increased in the initial phase, and the maximum tolerated dose was maintained in the maintenance phase for 3 years.

Evaluations

Scales: Demographic data and baseline characteristics of the patients were collected. Patients with preoperative nasal symptoms such as nasal congestion and purulent discharge within one year after surgery, or polyps found during nasal endoscopy, are recorded as relapse. Preoperative, the 3rd month, the 6th month, and the 1st year after ESS, visual analog scale (VAS) scoring, sino-nasal outcome test-22 (SNOT-22) scoring, and total nasal symptom score (TNSS) were performed to evaluate the postoperative dynamic changes of patients' conditions subjectively, calculate the difference between the postoperative score and the baseline score, and compare the differences among groups.

Electron microscopy: Part of the nasal mucosa specimens of the surgical side were obtained before and 1 year after surgery for transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Observe the epithelial cell condition to evaluate respiratory tract inflammation, observe cilia microstructure to evaluate epithelialization of the mucosa, and the differences among the groups were compared.

Inflammatory mediators: The other part of the nasal mucosa was tested by ELISA (China, Westang) for the expression levels of the relevant inflammatory factors including eosinophil cationic protein (ECP), IL-8, IFN-γ, IL-25, IL-33, and IL-17. Make the nasal mucosa tissue homogenate. The ELISA detection operates according to the instructions. Compare the difference between patients who relapsed and non-relapsed before treatment, and the difference among different treatment groups after treatment.

Statistical Analysis

All statistical analyses were performed on SPSS Statistics 22.0. One-way analysis of variance was used to compare the differences of the scores and differences in the expression levels of inflammatory mediators among the groups. If the *p*-value is less than 0.05, the difference is considered significant.

RESULTS

Of the 64 patients, 11 were out of contact and 53 were eventually included. There was no significant difference among groups regarding demographic data and baseline characteristics (Table 1).

Comparison of Scoring between 3 Groups

One year after surgery, 4 people in group A had preoperative symptoms such as nasal congestion and nasal mucous secretions. Among them, 1 patient had polyps and the recurrence rate was 22.2%. Two people in group B had relapse symptoms, with a relapse rate of 10%. No one in group C had relapse symptoms.

Preoperative, the 3rd month, the 6th month, and the 1st year after ESS, VAS scoring, SNOT-22 scoring, TNSS were collected, and differences between postoperative and baseline scores were calculated. We found that there was no significant difference in the scores of the 3 groups in the third month after the surgery. In the 6th month, VAS and SNOT-22 scoring were significantly different among the 3 groups, while TNSS was not significantly different. In the first year after the operation, there was a significant difference in the three scores among the three groups (Figure 1).

Table 1. Demographic data and baseline characteristics in 3 groups

Group	N	Age	Gender(F/M)	AA%	History of ESS	Lund-Mackay CT Score
M	18	41.7(20-64)	5/13	22.2%	16.7%	11.58±4.95
M+NI	20	41.1(23-61)	7/13	30.0%	40.0%	10.92±5.05
M+NI+SIT	15	31.6(18-50)	4/11	20.0%	26.7%	1

AA%: prevalence of allergic asthma; M: medication, M+NI: medication + nasal irrigation,
M+NI+SIT: medication + nasal irrigation + specific immunotherapy, ESS; endoscopic sinus surgery

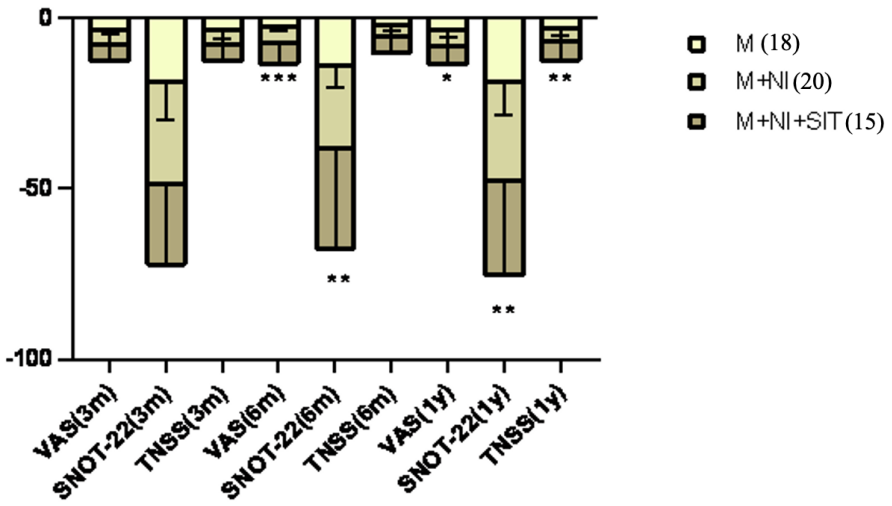

Figure 1. Comparison of VAS, SNOT-22, TNSS in 3 groups. VAS: visual analog scale scoring, SNOT-22: sino-nasal outcome test-22 scoring, TNSS: total nasal symptom score. M(N=18): medication, M+NI (N=20): medication + nasal irrigation, M+NI+SIT(N=15): medication +nasal irrigation +specific immunotherapy, *p<0.05, **p<0.01, ***p<0.005, compared by one-way analysis of variance.

There was no significant difference in the scores of the 3 groups in the third month after the ESS. In the 6th month, VAS and SNOT-22 scoring were significantly different among the 3 groups, while TNSS was not significantly different. In the first year after the operation, there was a significant difference in the three scores among the three groups.

Electron Microscopy Results

TEM analysis revealed that the epithelial cells of the nasal mucosa were arranged disorderly and sparsely before surgery, and necrotic cells were seen, accompanied by neutrophil infiltration (Figure 2). One year after ESS, the epithelial cells of the nasal mucosa in group A were arranged in a disordered manner, with short microvilli visible. The cilia can be seen and the structure of microtubules was abnormal. The epithelial cells of nasal mucosa in group B were arranged more orderly and scattered with necrotic cells. The epithelial cells of the nasal mucosa in group C were arranged neatly, with phagocytes visible.

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The arrangement of cilia in the nasal mucosa in group C was more orderly than that in group B, one year after ESS (Figure 3).

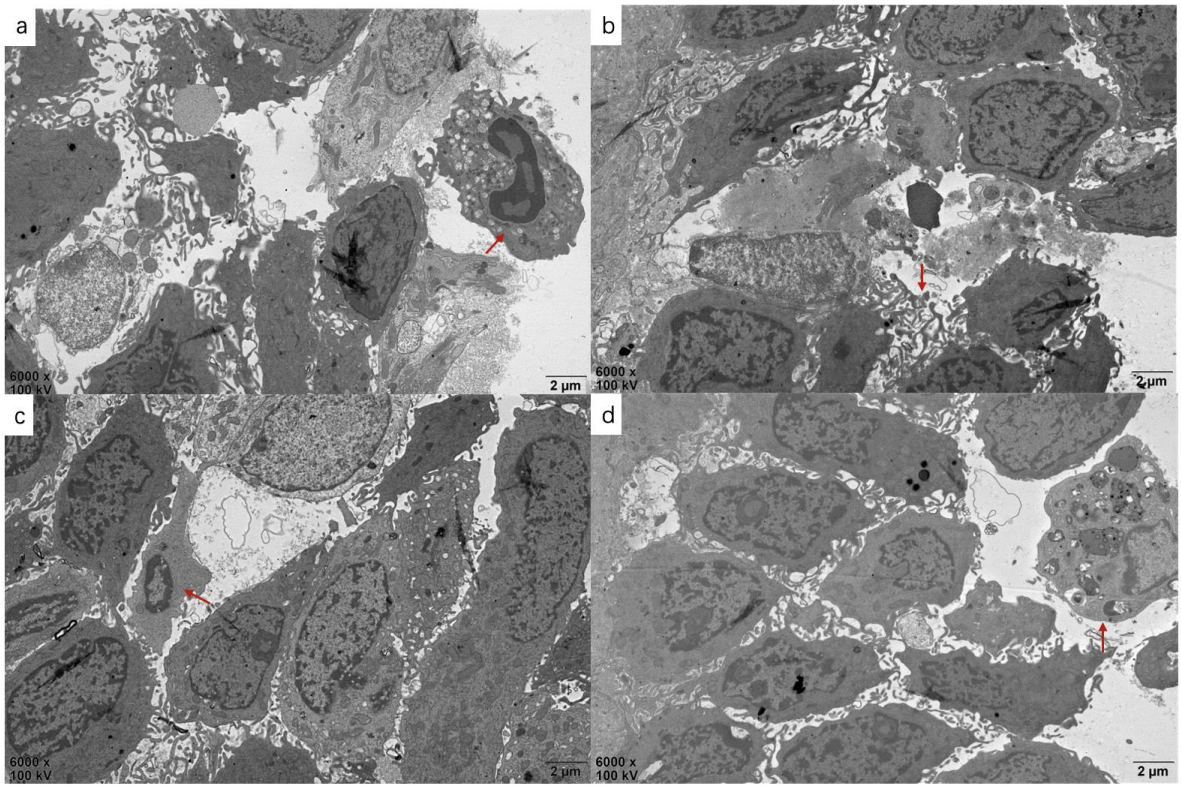

Figure 2. Transmission electron microscopy (TEM) of the nasal mucosa of 3 groups before and 1year after endoscopic sinus surgery (ESS) (6000X, 10kV). a: nasal mucosa before ESS, The epithelial cells of the nasal mucosa were arranged disorderly and sparsely before surgery, and necrotic cells were seen, accompanied by neutrophil infiltration. b: nasal mucosa of group A (medication) after ESS, the epithelial cells were arranged in a disordered manner, with short microvilli visible. c: nasal mucosa of group B (medication + nasal irrigation) after ESS, The epithelial cells were arranged more orderly and scattered with necrotic cells. e: nasal mucosa of group C (medication +nasal irrigation +specific immunotherapy) after ESS, the epithelial cells were arranged neatly, with phagocytes visible.

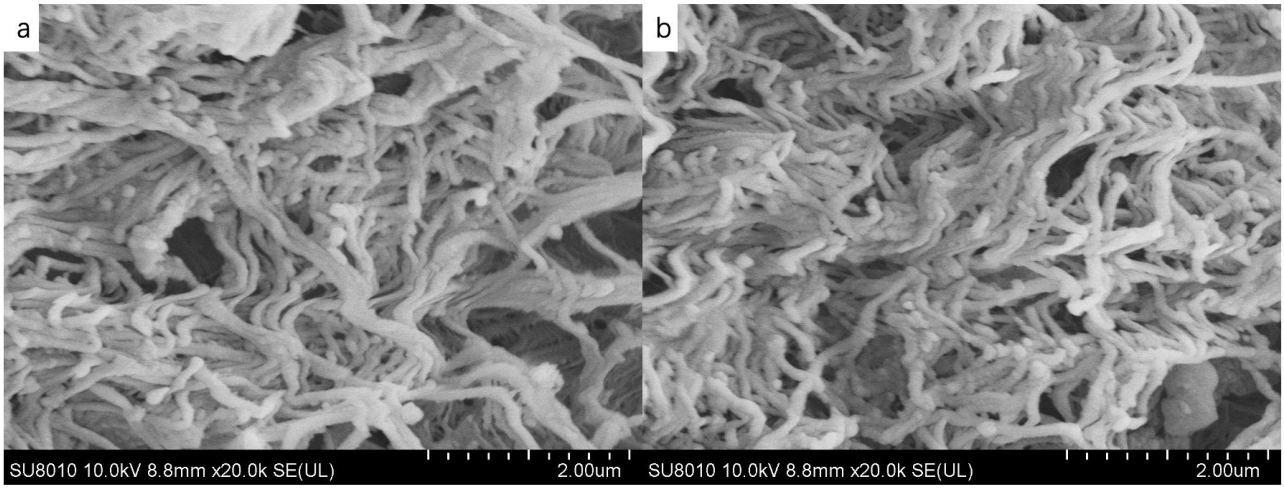

Figure 3. Scanning electron microscopy (SEM) of the nasal mucosa of group B and C 1 year after endoscopic sinus surgery (ESS) (2.00 µm, 10.0kV). a: group B (medication + nasal irrigation), b: group C (medication +nasal irrigation +specific immunotherapy)

Comparison of Expression Levels of Inflammatory Mediators

Of the 64 cases included, 14 patients had a history of ESS surgery, which was considered as recurrence group, and 50 patients were the first time to receive the surgery which was considered as a non-recurrence group. The expression levels in the nasal mucosa tissue homogenate of the two groups are shown in Table 1. It can be seen that the expression levels of ECP and IL-17 in the nasal mucosa of the recurrence group are higher than that of the non-recurrence group, and the differences are statistically significant. There was no significant difference in the expression levels of IL-8, IFN-γ, IL-25, and IL-33 between the two groups (Table 2).

Table 2. Comparison of expression levels of eosinophil cationic protein (ECP), IL-8, IFN-γ, IL-25, IL-33, and IL17 in the nasal mucosa of recurrence group and non-recurrence group（pg/ml, $\bar{x}$±s）

	N	ECP	IL-8	IFN-γ	IL-25	IL-33
recurrence	14	2414.32±896.21	322.35±44.82	15.95±6.20	147.05±59.75	984.76±90.67
non- recurrence	50	1646.05±351.28	247.11±73.65	9.82±7.34	91.99±46.36	1183.70±64.79
p		**0.004***	0.317	0.137	0.109	0.429

* significant difference, $p<0.05$

There was no significant difference in the expression levels of inflammatory mediators in each treatment group before surgery ($p>0.05$). One year after surgery, the expression levels of ECP, IL-8, and IL-17 in the nasal mucosa of group B were lower than those in group A ($p<0.05$); The expression levels of IL-8, IL-25, IL-33, and IL-17 in group C were lower than those in group A ($p<0.05$); and the expression levels of nasal mucosa ECP, IL-25, and IL-17 in group C were lower than those in group B (Table 3).

Table 3. Comparison of expression levels of eosinophil cationic protein (ECP), IL-8, IFN-γ, IL-25, IL-33 and IL17 in nasal mucosa indifferent treatment groups（ pg/ml, $\bar{x}$±s ）

	N	ECP	IL-8	IFN-γ	IL-25	IL-33	IL-17
M	18	1456.67±286.23	288.67±84.62	12.45±6.47	177.35±52.63	1048.70±91.56	42.67±8.44
M+NI	20	793.35±109.34	167.13±33.57	16.59±7.83	152.89±46.64	932.01±44.72	37.89±8.73
M+NI+SIT	15	511.28±43.44	158.62±42.78	14.32±8.21	77.61±54.48	517.33±52.77	21.32±5.90
Pa		**0.009***	**0.012***	0.144	0.117	**0.452***	**0.048***
Pb		**0.003***	**0.010***	0.324	**0.025***	**0.022***	**0.013***
Pc		**0.047***	0.068	0.355	**0.038***	0.058	**0.022***

* significant difference. $p<0.05$. M: medication, M+NI: medication + nasal irrigation, M+NI+SIT: medication + nasal irrigation + specific immunotherapy. Pa: M group vs M + NI group, Pb: M group vs M + NI + SIT group, Pc: M + NI group vs M + NI + SIT group

DISCUSSION

In this study, we found that for patients with CRS and AR, the prognosis of CRS adding nasal irrigation to conventional treatment is better than that of conventional medical treatment alone. Nasal irrigation combined with SCIT is superior to nasal irrigation combined with medication, and the recurrence rate is significantly reduced. In the third month after surgery, there was no significant difference in the scores of the three groups. At 6 months, the VAS score and SNOT-22 score were significantly different among the three groups, while TNSS was not significantly different. One year after surgery, there were significant differences in the three scores among the three groups. At the same time, when patients were included, the

recurrent patients had significantly higher expression levels of ECP and IL-17 in their nasal mucosa than those in the first surgery. Each group received different treatment options after ESS. The expression levels of ECP, IL-8, and IL-17 in the nasal mucosa of group B, one year after surgery were lower than that of group A; The expression levels of ECP, IL-8, IL-25, IL-33, and IL-17 in the nasal mucosa of the group C were lower than that of group A; and the expression levels of nasal mucosa ECP, IL-25 and IL-17 in group C were lower than that of group B.

The European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS2012)[13] recommends the use of intranasal steroids, macrolides, and nasal irrigation after ESS to improve the inflammatory response of the nasal cavity and sinus mucosa, improve the prognosis of chronic sinusitis and reduce the recurrence rate. Nasal irrigation uses hypertonic dehydration to reduce edema of the nasal cavity and sinus mucosa; disintegrate scabs, form soluble chelates with pollutants in the nasal cavity and discharge through the lotion; dilute nasal sinus mucus and inhibit bacterial growth; maintain a moist nasal environment14.[15,16] According to the electron micrograph in this study, it can be found that SIT supplemented with nasal cavity irrigation can effectively promote postoperative nasal mucosal epithelialization and recovery of cilia morphology. Existing studies have shown that rinse the nasal cavity with larger doses and higher pH after ESS can promote the mucosal epithelialization of the surgical cavity and the recovery of nasal function.[17,18] SIT can significantly improve allergy symptoms, reduce the use of drugs and improve the quality of life of patients, and has better long-term effects than symptomatic drug treatment. Studies have found that in a non-randomized controlled trial, the symptom scores of patients with CRS who received SIT were significantly improved compared with those of baseline and control patients.[19] In this study, the difference in TNSS occurred later than the other two scores, which may be because the treatment process of SCIT was longer and the onset time was later. Therefore, regardless of whether or not to accept SCIT, nasal irrigation and drug treatment should be used after surgery.

We found that in CRS patients with AR, the expression levels of ECP and IL-17 in the nasal mucosa of patients with recurrence or non-recurrence are different, while IL-8, IFN-γ, IL-25, IL -33 have no obvious difference. ECP level of the nasal mucosa can be regarded as a marker of eosinophil activity. The inflammatory response of these patients is mainly activated eosinophil, and ECP concentration is related to the degree of eosinophil inflammation.[20] Previous studies have found that infiltration of eosinophil can reconstruct the nasal mucosa tissue and promote the formation of CRS nasal polyps.[21] IL-17 is the main effector of Th17 cells, reflecting the activity of Th17 cells. Studies have shown that the expression of IL-17 in nasal polyps is higher than that in the uncinate process.[22] IL-17 can increase the expression of the remodeling factor MUC5B mucin,[23] it can also promote the expression of metalloproteinases-9 (MMP-9) by activating the NF-κB signaling pathway and rebuild CRS tissue.[24] IL-8 represents the chemotaxis of neutrophils; IFN-γ is the main effector of Th1 type immune response; IL-25 is one of the members of the IL-17 cytokine family, which can participate in type 2 immune response, its role in allergic diseases (asthma, etc.) has also been confirmed.[25] IL-33 is an important immunomodulator in multiple activities of type 2, type 1, and regulation of immune response, and also plays an important role in allergic, fibrotic, infectious, and chronic inflammatory diseases.[26] In this study, the higher expression levels of ECP and IL-17 in patients with recurrence indicate that a more severe immune imbalance is more likely to cause CRS to relapse. One year after surgery, the expression levels of ECP, IL-25, IL-33, and IL17 in group C were reduced, indicating that SIT may control the progress of AR by down-regulating Th2 and Th17 type responses to improve the prognosis of CRS with AR. In addition, nasal irrigation after CRS can also reduce the expression level of IL-8, which may be accompanied by a reduction in neutrophil chemotaxis to achieve local immune regulation.

The relationship between AR and CRS is close.[27] Airway allergic factors in CRS promote the pathological changes and postoperative recurrence of CRS by aggravating the immune imbalance, making CRS lingering. Tomassen et al28 found that CRS endotypes can be divided into 5 categories through hierarchical cluster analysis of variables, which are driven by 5 groups of related cytokines: (1) eosinophilic, Th2-driven inflammation markers (ECP, IL-5, IgE, SE-IgE), and antibody and albumin production; (2) neutrophils and proinflammatory cytokines (IL-1b, IL-6, IL-8, MPO); (3) Th17 Or Th22 related markers (IL-17A, IL-22, TNF-α); (4) Th1

marker: IFN-γ. (5) TGF-β1. The degree of eosinophil infiltration and type 2 inflammation is related to the severity of CRS, asthma comorbidities, and postoperative disease recurrence.[29] AR is also an imbalance of the Th cell network composed of Th1/Th2/Th17/Treg characterized by enhanced Th2 response. It is closely related to airway allergic disease, and it is a chronic inflammation mediated by specific IgE. Specific immunotherapy is effective in patients with allergic rhinitis and asthma, with improved clinical symptoms and a reduction in the number of effector cells in the target organ, including mast cells, basophils, eosinophils, and type 2 congenital lymphoid cells.[30] Therefore, it can be concluded that for CRS patients with AR, SIT can improve the prognosis of CRS. Despite the lack of high-quality evidence to confirm the clinical efficacy of nasal irrigation, nasal irrigation is usually recommended in CRS patients after ESS.[31] There is currently no consensus on the frequency of nasal irrigation of CRS, treatment time, device type and amount of solution to be used, and further high-quality comparative studies are needed.

In this study, it can be seen that the combination of specific subcutaneous immunotherapy and nasal irrigation can improve the outcome of patients with CRS and AR 1 year after ESS. The long-term effects still need further study.

In summary, specific immunotherapy combined with nasal irrigation can reduce the recurrence rate of CRSwAR patients after ESS, improve patients' symptoms and quality of life; promote the epithelialization of the mucosa in the surgical cavity; adjust the local immune response of the nasal cavity and improve the inflammatory response; thus can improve patients after ESS The prognosis of 1 year.

CONFLICT OF INTEREST

The authors declare that no financial or other conflicts of interest exist concerning the content of the article.

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