REVIEW

Recent advances in the management of allergic rhinitis

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Abstract : Allergic rhinitis (AR) is a type I allergic disease characterized by sneezing, watery rhinorrhea, and nasal obstruction. An epidemiological survey found that approximately 50% of Japanese individuals have AR. Histamine is a major chemical mediator that induces AR symptoms through its binding to histamine H_1 receptor (H1R). We demonstrated that antihistamines have a blocking effect on histamine signaling of H1R, and the suppressive effect on histamine-induced up-regulation of transcriptional activation, and the suppressive effect on basal transcription of H1R in the absence of histamine which may be part of the inverse agonist action of antihistamine. Sublingual immunotherapy (SLIT) with a standardized Japanese cedar (JC) pollen significantly improved nasal symptoms and AR-related sleep disturbance in patients with JC pollinosis. Dual SLIT with JC pollen and house dust mites (HDM) suppressed both JC pollen-induced seasonal and HDM-induced perennial nasal symptoms in bisensitized patients with AR. Dual SLIT was more effective in suppressing nasal obstruction at the peak JC pollen period than mono SLIT with JC pollen. Posterior nasal neurectomy (PNN) improved nasal symptoms and medication scores in patients with severe perennial AR. Herein, we describe recent advances in the management of AR. J. Med. Invest. 72 : 14-20, February, 2025

Keywords **:** *allergic rhinitis, histamine H_1 receptor, interleukin-9, sublingual immunotherapy, posterior nasal neurectomy*

INTRODUCTION

Allergic rhinitis (AR) is a global health problem with increasing prevalence and is associated with an enormous medical burden. AR is a type I allergic disease of the nasal mucosa characterized by paroxysmal and repetitive sneezing, watery rhinorrhea, and nasal blockage (1). Previous studies reported the role of immune cells, such as group 2 innate lymphocytes (ILC2s), T helper 2 (Th2) cells, follicular helper T cells, follicular regulatory T cells, regulatory T cells, B cells, dendritic cells, and epithelial cells, in AR pathogenesis (2, 3).

Japanese cedar pollinosis (JCP) is the most prevalent AR in Japan. The number of patients with JCP has markedly increased over the last two decades. Spontaneous remission is rare (4) ; therefore, a lot of patients suffer from nasal and ocular allergic symptoms for a long time. Currently, one in two Japanese people suffers from AR. A recent epidemiological study revealed a marked increase in the prevalence of AR (29.8%, 39.4%, and 49.2% in 1998, 2008 and 2019, respectively). In particular, the number of patients with JCP has increased, with a prevalence of 16.2% in 1998, 26.5% in 2008, and 38.8% in 2019, and 49.5% of people aged 10-19 years developed JCP in 2019. Additionally, the prevalence of perennial AR, mainly due to mite antigens, has increased with a prevalence of 18.7% in 1998, 23.4% in 2008, and 24.5% in 2019 (1).

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MECHANISMS OF AR

In response to antigen entry into the nasal mucous membrane, IgE is produced in the nasal mucosa and regional lymphatic tissues as a result of the type 2 immune response by Th2 cells and ILC2s (3). Th2 cells, which produce IL-4, IL-5, and IL-13 in response to antigens, play a significant role in its pathogenesis by inducing a type 2 immune response. Recent discoveries surrounding ILC2s have revealed their production of type 2 cytokines in response to IL-25, IL-33, and TSLP released from epithelial cells. These findings suggest the involvement of ILC2s in the development of AR. In sensitized individuals, inhaled antigens pass through the nasal mucosal epithelial cells to bind to IgE on mast cells distributed in the superficial layer of the nasal mucosa. In response to an antigen antibody reaction, chemical mediators, such as histamine and leukotrienes (LTs), are released from mast cells. They stimulate the sensory nerve endings and blood vessels of the nasal mucosa causing sneezing, watery rhinorrhea, and nasal obstruction as an early phase reaction. Then, various inflammatory cells, such as activated eosinophils, infiltrate the nasal mucosa in response to cytokines, chemical mediators, and chemokines. LTs produced by these inflammatory cells cause nasal obstruction as a late phase reaction, which occurs 6-10 h after antigen exposure (1).

Sneezing is triggered by histamine binding to H1R on the trigeminal nerve in the nasal mucosa. The afferent signal is transmitted to the sneezing center, which leads to the sneezing reflex. In addition to the sneezing reflex, sensory nerve stimulation in the nasal mucosa induces the parasympathetic nerve reflex leading to the release of acetylcholine, which binds to muscarinic acetylcholine receptors in the nasal gland. Although histamine acts directly on the nasal mucosal vessels, causing plasma leakage, most rhinorrhea secretions originate from the nasal glands. Nasal mucosal swelling results from edema caused by plasma leakage and vessel dilation. The direct action of chemical

mediators, such as histamine, platelet-activating factor, PGD2, kinins, and LTs, is important in this process. Among these, LTs released from infiltrating inflammatory cells, particularly eosinophils, have an important role in the observed nasal mucosal swelling in the late-phase reaction. Continuous antigen exposure causes nonspecific hypersensitivity and irreversible nasal mucosal hypertrophy (Fig. 1) (1).

TREATMENT OF AR

Pharmacotherapy

1) Second-generation antihistamines

The indication of second-generation antihistamines is treatment of the mild-to-moderate sneezing/rhinorrhea type. They are often used with nasal steroids depending on severity. Histamine is a major chemical mediator in the development of AR that induces nasal allergy symptoms through binding to H1R. The strength of the histamine signaling that is involved in nasal symptoms depends on H1R expression level (5). The expression of H1R mRNA is up-regulated in the nasal mucosa of patients with pollinosis (6, 7). Our group reported that the H1R gene was upregulated in the nasal mucosa of patients with pollinosis, and the expression level of H1R was strongly correlated with the severity of the nasal symptoms in AR (8). Moreover, we found that histamine-mediated stimulation of H1R induced upregulation of the H1R gene through protein kinase Cδ (PKCδ) activation, and that the elevated receptor expression levels in the nasal mucosa increased histamine signaling to further exacerbate the symptoms of AR (9).

Antihistamines are H1R antagonists and are effective for AR treatment, including pollinosis. In Japan, prophylactic administration of antihistamines before the onset of pollen season is recommended for pollinosis treatment (1). A previous study reported that the pre-seasonal administration of antihistamines is more effective than post-onset administration in patients with pollinosis (10). Our group reported that histamine increased the expression of H1R mRNA, whereas antihistamine suppressed its up-regulation (9). Using a toluene-2,4-diisocynate (TDI)-sensitized rat model, we found that intranasal application of TDI to the nasal mucosa induced nasal symptoms together with an increase of H1R mRNA level in the nasal mucosa, whereas antihistamine suppressed these effects (11). Moreover, prophylactic administration of antihistamines decreased H1R gene up-regulation with suppression of nasal symptoms (8). We examined the effects of antihistamine on the up-regulation of H1R mRNA in the nasal mucosa of patients with JCP induced by controlled exposure to JC pollen using an environmental exposure unit (EEU). We found that controlled exposure to JC pollen induced both nasal symptoms and up-regulation of H1R mRNA in the nasal mucosa of responder patients with JCP, and prophylactic administration of an inverse agonist of H1R suppressed both pollen exposure-induced nasal symptoms and up-regulation of nasal H1R mRNA. Moreover, prophylactic administration with an inverse agonist of H1R down-regulated basal gene expression of H1R mRNA in the nasal mucosa without pollen exposure. Our previous studies reported that antihistamines exhibiting inverse agonistic activity alleviate nasal symptoms in pollinosis patients through three distinct mechanisms : blocking histamine effects on H1R, suppressing histamine-induced transcriptional activation of H1R, and inhibiting basal transcription of H1R in the absence of histamine (12-15).

2) Intranasal corticosteroid

Intranasal corticosteroid (INCS) is highly effective for sneezing, watery rhinorrhea, and nasal blockage. INCS is poorly absorbed with few systemic adverse effects. We reported that dexamethasone significantly reduced both nasal symptoms and the upregulation of H1R and histidine decarboxylase (HDC) in the nasal mucosa of rats sensitized and induced by TDI (16, 17). It is suggested that the therapeutic effects of dexamethasone are, in part, due to its suppressive effects on the upregulation of H1R

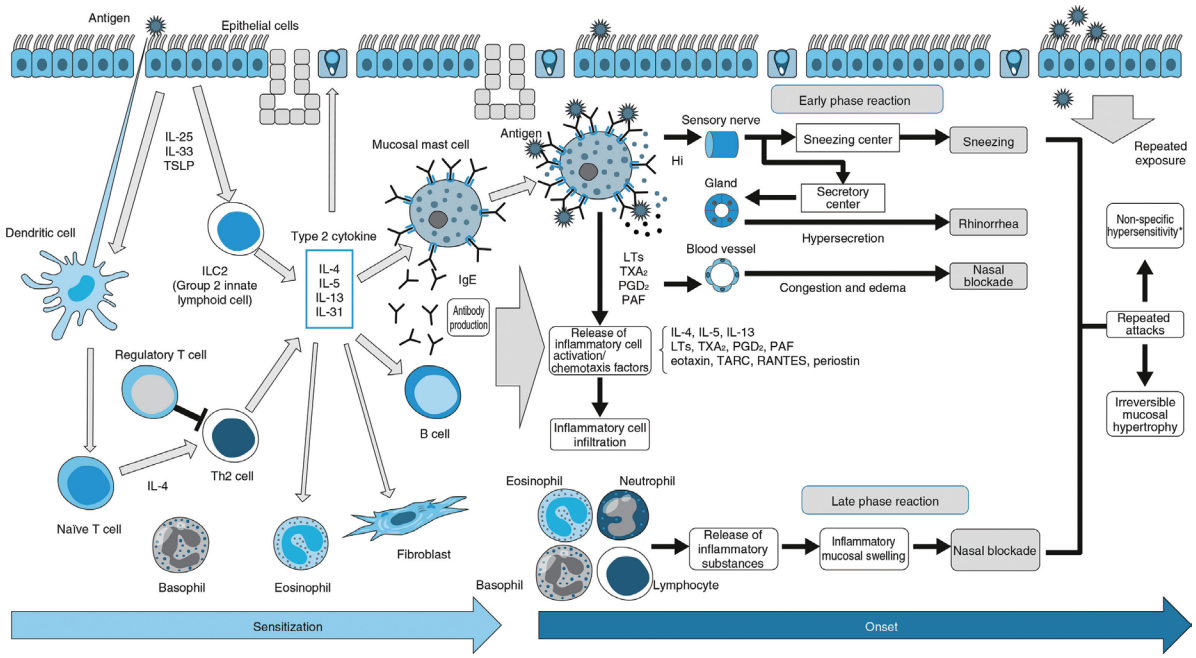

Figure 1. Pathogenic mechanism of allergic rhinitis.
Hi, histamine ; LTs, leukotriene ; TXA2, thromboxane A2 ; PGD2, prostaglandin D2 ; PAF, platelet-activating factor ; IL, interleukin ; TARC, thymus and activation-regulated chemokine ; RANTES, regulated upon activation normal T expressed, and presumably secreted ; TSLP, thymic stromal lymphopoietin.

and HDC. Furthermore, A randomized placebo-controlled trial reported that pre-seasonal prophylactic administration of INCS prevented exacerbation of nasal symptoms during the peak pollen season in patients with pollinosis (18). We reported that INCS down-regulated H1R gene expression in the nasal mucosa of healthy participants with no history of AR and that dexamethasone, a corticosteroid, inhibited both basal transcription and histamine-induced transcriptional activation of H1R in HeLa cells through suppression of extracellular signal-regulated kinase (ERK) phosphorylation in the PKCδ/ERK/PARP-1 signaling involved in H1R gene transcription (Figs. 2, 3) (19, 20). These findings suggest that pre-seasonal prophylactic administration of INCS suppresses the basal and pollen-induced up-regulation of H1R gene expression in the nasal mucosa of patients with pollinosis, thereby preventing the exacerbation of nasal symptoms during the peak pollen season (21).

3) LT receptor antagonists

LTs produced and released by mast cells, eosinophils, and macrophages have relaxing effects on the vascular smooth muscles of the nasal mucosa, thereby enhancing vascular permeability and stimulating eosinophil migration. The indications for LT receptor antagonists (antiLTs) include mild-to-moderate nasal blockage type and combined type with nasal blockage as the primary complaint (1). Previous studies reported that combination therapy of antihistamines and antiLTs was more effective in alleviating nasal symptoms than either treatment alone (22, 23) ; moreover, we reported that compared to the effect of individual drugs, the combination therapy with antiLTs and antihistamine is more effective for the suppression of the up-regulation of H1R mRNA, thereby treating nasal hypersensitivity symptoms using an AR rat model (24). As antiLTs suppress H1R signaling, this mechanism may explain the additive therapeutic effects from the combined treatment.

4) Th2 cytokine inhibitor

Suplatast tosilate inhibits Th2 cytokine production, including IL-4 and IL-5 from T lymphocytes, to alleviate allergic inflammation. We reported that treatment with suplatast in combination with an antihistamine markedly alleviated nasal symptoms in an animal model of AR (25). We also reported that suplatast suppressed both TDI-induced upregulation of the IL-9 gene in the nasal mucosa of TDI-sensitized rats and ionomycin-induced nuclear factor of activated T cells (NFAT) signaling-mediated IL-9 mRNA upregulation in RBL-2H3 cells (26). These findings suggest that NFAT-mediated upregulation of IL-9 gene expression is involved in the AR pathogenesis, in addition to upregulation of H1R, and that suplatast suppresses NFAT-mediated signaling to alleviate the symptoms of AR.

We identified pyrogallol from the extract of Awa tea, a local fermented tea, and proanthocyanidin (LRPC) containing a gallocatechin tetramer from the extract of local Bittyu lotus root

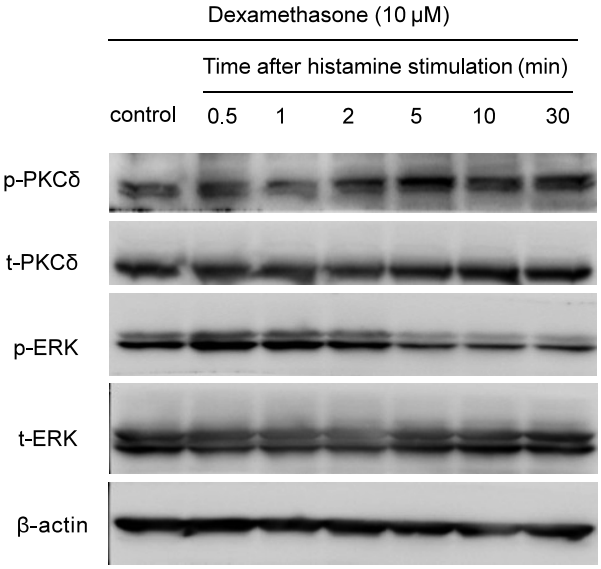

Figure 3. Effects of dexamethasone on histamine-induced phosphorylation of PKCδ and ERK in HeLa cells.
HeLa cells were serum-starved for 24 h. The cells were treated with 10 μM dexamethasone for 1 h before stimulation with 100 μM histamine and phosphorylation levels of PKCδ and ERK at various timepoints were determined using immunoblot analysis. In the presence of dexamethasone, the density of p-ERK decreased over time, whereas p-PKC increased following treatment with histamine. p-PKCδ : phospho PKCδ ; t-PKCδ : total PKCδ ; p-ERK : phospho ERK ; t-ERK : total ERK.

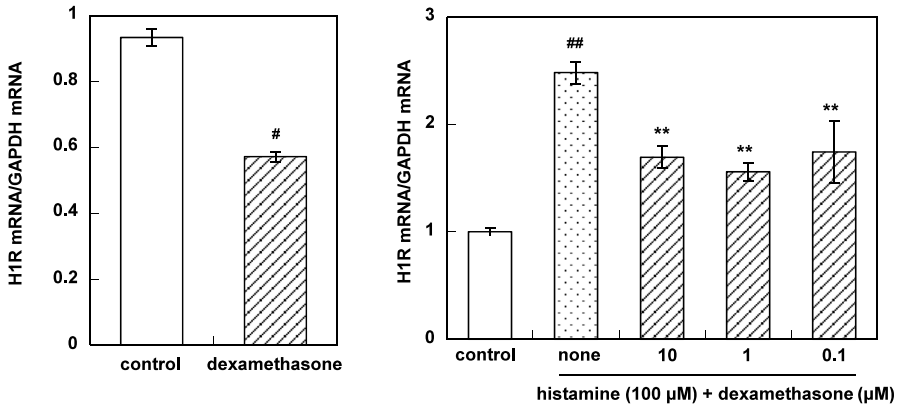

Figure 2. Effects of dexamethasone on basal (A) and histamine-induced (B) H1R mRNA levels in HeLa cells.
(A) HeLa cells were treated with dexamethasone (1 μM) for 1 h. (B) HeLa cells were treated with dexamethasone (0.1-10 μM) for 1 h before 100 μM histamine treatment for 3 h. Then, the cells were harvested, and total RNA was isolated. Amount of H1R mRNA was determined by quantitative RT-PCR. Data are presented as means ± SEM (n = 3-9). **, $p < 0.01$ versus histamine ; ##, $p < 0.01$, #, $p < 0.05$ versus control.

as anti-allergic compounds. Both pyrogallol and LRPC may suppress NFAT-mediated upregulation of IL-9 gene expression and alleviate the symptoms of AR ; thus, NFAT-mediated signaling may be a novel treatment target (27, 28).

5) Anti-IgE antibody

Omalizumab was approved for the treatment of severe and severest seasonal AR in 2019, based on a clinical trial in which omalizumab was added to the concomitant antihistamine and INCS administration improved the symptoms and QOL of patients compared to placebo in Japan (29). Indications for omalizumab are age ≥ 12 years old, serum specific IgE against Japanese cedar pollen ≥ class 3 (3.5 UA/ml in the FEIA or 13.5 lumicount by CLEIA), and severe symptoms persisting more than one week despite treatment with chemical mediator receptor antagonists and INCS in addition to elimination and avoidance of antigens.

6) Herbal medicines

Syo-seiryu-to (SST) is a traditional herbal medicine that has been used clinically to treat AR in Japan. SST improves acute symptoms, such as sneezing and rhinorrhea, as well as chronic symptoms, such as nasal obstruction, in patients with AR. We reported that SST suppressed nasal symptoms and gene expression of H1R, histidine decarboxylase, and Th2-cytokines, including IL-4, 5, in the nasal mucosa of AR model rats (30). Moreover, we demonstrated that SST and its crude drugs, except for Pinellia tuber, significantly and dose-dependently suppressed PMA-induced IL-33 and H1R mRNA up-regulation in vitro, and Ephedra herb and cinnamon bark had the strongest effect on them.

The half-maximal inhibitory concentration values of the seven crude drugs used to inhibit PMA-induced IL-33 mRNA up-regulation are correlated with those related to H1R mRNA up-regulation, suggesting that they act on a common signal molecule (31). These findings suggest that SST improves the nasal congestion that is induced by IL-33-related eosinophil infiltration and inhibits sneezing and rhinorrhea that are induced by H1R-mediated histamine signaling in the nasal mucosa of AR patients through its inhibition of a common molecule in the gene expression pathways of IL-33 and H1R.

ALLERGEN IMMUNOTHERAPY

Allergen immunotherapy (AIT) has been used over the past century. Continuous treatment is required for 3 years to achieve long-term clinical remission. AIT can provide long-term benefits in patients with AR by modulating the immune response. After AIT, local mast cells are decreased, Th1/Th2 balance is altered, and regulatory T and B cells are increased. Pharmacotherapy for AR provides relief from symptoms but does not modify or cure the disease. In contrast, AIT can alter the natural course of AR (32).

Sublingual immunotherapy (SLIT) was approved in Japan for AR of JCP and house dust mites (HDM) (33, 34). A previous study reported that 38% of patients with JCP complained of sleep problems (35). We reported that SLIT with JC pollen drops suppressed nasal symptoms in patients with JCP, leading to improvements in AR-related sleep disturbance and daytime troubles with daily life (36). One-year treatment of SLIT with JCP tablets was more effective for alleviating nasal symptoms and AR-related sleep disturbance than 2-year treatment of SLIT with JCP drops and prophylactic treatment with antihistamines (Figs. 4, 5) (37). SLIT with JCP tablets and drops were administrated at the maintenance doses of 5000 and 2000 JAU/day respectively. Because it was reported that SLIT with JCP antigens for a year suppressed nasal symptoms at the peak pollen period

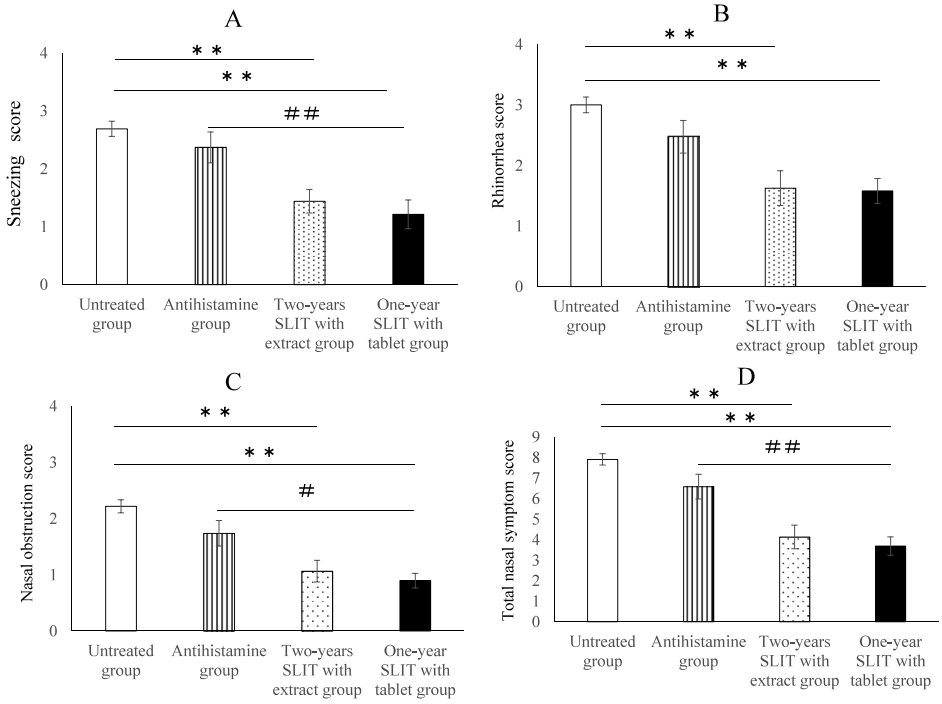

Figure 4. Effect of SLIT with JC pollen tablets on nasal symptoms in patients with JCP. Comparison of sneezing (A), rhinorrhea (B), nasal obstruction (C), and total nasal symptom score (D) in 2019 during the JCP dispersal period. Data are presented as mean ± SEM. **p < 0.01 vs. untreated group. ##p < 0.01, #p < 0.05 vs. antihistamine group.

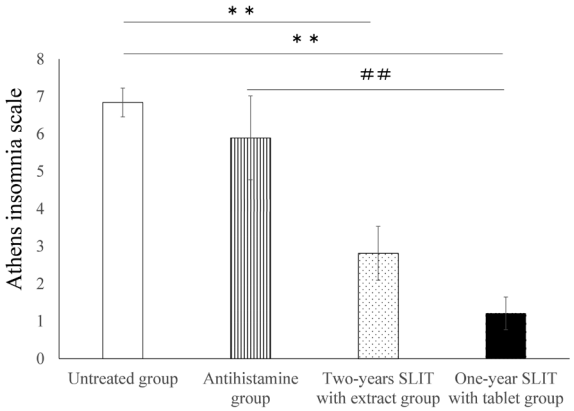

Figure 5. Effect of SLIT with JC pollen tablets on sleep disturbance in patients with JCP. Data are presented as mean ± SEM. **p < 0.01 vs. untreated group. ##p < 0.01 vs. antihistamine group.

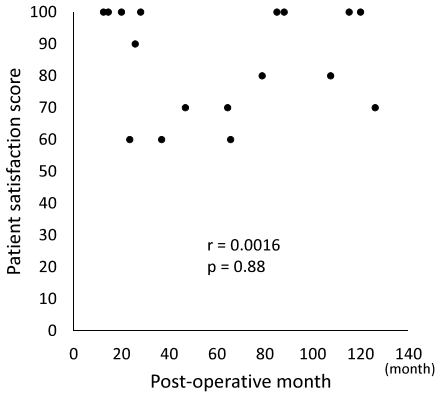

Figure 6. Correlation between patient satisfaction and postoperative month. No correlation was found between patient satisfaction with surgery and postoperative period (r = 0.0016, p = 0.88).

Table 1. Patient characteristics and preoperative and postoperative scores of rhinorrhea, sneezing, nasal obstruction, TNSS, medication, overall nasal symptom and patient satisfaction.

	Total		within 5 year		more than 5 year	
Number of patients (male : female)	17 (12 : 5)		8 (4 : 4)		9 (8 : 1)	
Age	31.5 ± 18.1		31.6 ± 15.7		31.4 ±20.9	
post-operative month	62.1 ± 39.5		30.3 ± 16.6		98.0 ± 22.0	
Scores	pre-ope	post-ope	pre-ope	post-ope	pre-ope	post-ope
Rhinorrhea	3.5 ± 1.0	1.5 ± 1.5	3.5 ± 1.1	1.0 ± 1.4	3.6 ± 1.0	2.0 ± 1.5
Sneezing	1.8 ± 1.6	0.5 ± 1.0	2.0 ± 1.7	0.3 ± 0.5	1.6 ± 1.6	0.7 ± 1.3
Nasal obstruction	2.9 ± 1.5	0.6 ± 0.9	2.9 ± 1.4	0.5 ± 1.0	2.9 ± 1.8	0.7 ± 0.9
TNSS	8.2 ± 2.7	2.6 ± 2.7	8.4 ± 2.8	1.8 ± 2.0	8.0 ± 2.8	3.3 ± 3.1
Medication	1.6 ± 1.4	0.4 ± 0.7	1.0 ± 1.3	0.3 ± 0.7	2.2 ± 1.3	0.4 ± 0.7
Overall nasal symptom	80.0 ± 17.0	23.5 ± 25.7	82.5 ± 17.5	16.3 ± 22.0	77.8 ± 17.2	30.0 ± 28.3
Patient satisfaction		84.7 ± 16.6		85.0 ± 18.5		84.4 ± 15.9

in a dose-dependent manner from 2000 to 5000 JAU/day (38), it is suggested that the dose-dependent efficacy of SLIT is responsible for the advantage of SLIT with JCP tablets over JCP drops.

We also reported that dual SLIT for JCP and HDM suppressed both JCP-induced seasonal and HDM-induced perennial nasal symptoms in bisensitized patients with AR, and dual-SLIT was more effective in suppressing nasal obstruction at peak pollen period than mono-SLIT with JCP (39). These findings suggest that dual-SLIT suppressed HDM-induced priming effects, resulting in further suppression of nasal obstruction at peak pollen period (39).

SURGICAL TREATMENT

Surgical treatment is recommended for patients with severe AR refractory to pharmacotherapy. We perform endoscopic posterior nasal neurectomy (PNN) to treat patients with severe perennial AR that is resistant to pharmacotherapy and corrective nasal cavity surgery for patients with nasal morphological abnormalities. Given that the posterior nasal nerves contain parasympathetic nerve fibers from the vidian nerve and sensory nerve fibers from the second branch of the trigeminal nerve, this suggests that PNN is effective in reducing rhinorrhea and sneezing (40, 41). Nasal obstruction is likely to be reduced by septoplasty and submucosal inferior turbinectomy. PNN was developed in Japan and numerous studies have confirmed the effectiveness of PNN ; however, there are few reports on its long-term prognosis (42, 43). We reported that PNN improved nasal symptoms and medication scores in patients with severe perennial AR, eliminating the need for continuous medication after surgery (Table 1) (44). We found no significant difference between patients with a postoperative period of < 5 years and those with > 5 years in terms of nasal symptoms, medication scores, and no correlation was found between patient satisfaction with surgery and postoperative period (Fig. 6), suggesting that the long-term effect of PNN for perennial AR lasts for > 5 years.

CONCLUSION

AR is a serious health problem that affects about half of the population of Japan. It causes nasal symptoms and affects quality of life. Although SLIT has been reported to have a therapeutic effect, its safety and long-term benefits, present therapies including pharmacotherapy and surgical treatment still do not offer sufficient relief for AR patients with increasing demand and prevalence. Further studies are needed to identify the immunological mechanism and biomarkers of SLIT, prevent antigen sensitization, and develop radical treatment.

CONFLICT OF INTEREST

The authors have no conflict of interest to disclose.

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