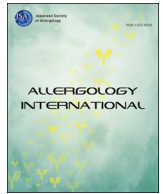




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Invited review article

Association and management of eosinophilic inflammation in upper and lower airways



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Abbreviations:

AERD, Aspirin-exacerbated respiratory disease; AR, Allergic rhinitis; BHR, Bronchial hyperresponsiveness; CRS, Chronic rhinosinusitis; ECRS, Eosinophilic chronic rhinosinusitis; INS, Intranasal corticosteroids; JCCP, Japanese cedar/cypress pollinosis; LT, Leukotriene; NP, Nasal polyps; PBMCs, Peripheral blood mononuclear cells; PEF, Peak expiratory flow; QOL, Quality of life; SCUADs, Severe chronic upper airway diseases; SCIT, Subcutaneous immunotherapy; SLIT, Sublingual immunotherapy

ABSTRACT

This review discussed the contribution of eosinophilic upper airway inflammation includes allergic rhinitis (AR) and chronic rhinosinusitis (CRS) to the pathophysiology and course of asthma, the representative counterpart in the lower airway. The presence of concomitant AR can affect the severity of asthma in patients who have both diseases; however, it is still debatable whether the presence of asthma affects the severity of AR. Hypersensitivity, obstruction and/or inflammation in the lower airway can be detected in patients with AR without awareness or diagnosis of asthma, and AR is known as a risk factor for the new onset of wheeze and asthma both in children and adults. Allergen immunotherapy, pharmacotherapy and surgery for AR can contribute to asthma control; however, a clear preventive effect on the new onset of asthma has been demonstrated only for immunotherapy. Pathological similarities such as epithelial shedding are also seen between asthma and CRS, especially eosinophilic CRS. Abnormal sinus findings on computed tomography are seen in the majority of asthmatic patients, and asthmatic patients with CRS show a significant impairment in Quality of Life (QOL) and pulmonary function as compared to those without CRS. Conversely, lower airway inflammation and dysfunction are seen in non-asthmatic patients with CRS. Treatments for CRS that include pharmacotherapy such as anti-leukotrienes, surgery, and aspirin desensitization show a beneficial effect on concomitant asthma. Acting as a gatekeeper of the united airways, the control of inflammation in the nose is crucial for improvement of the QOL of patients with co-existing AR/CRS and asthma.

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Introduction

Upper airway inflammation includes otitis media, rhinitis, rhinosinusitis, tonsillitis, and pharyngo-laryngitis. Due to the spread of guidelines and the development of new treatments, most of these diseases can be controlled by medical interventions including

patient education, pharmacotherapy, immunotherapy and surgery. On the other hand, some of these diseases are refractory to treatments and lead to a long-lasting impairment of the quality of life (QOL), the so called “severe chronic upper airway diseases” (SCUADs).¹ SCUADs include uncontrolled allergic rhinitis, eosinophilic rhinosinusitis, aspirin exacerbated respiratory disease, ciliary dyskinesia and cystic fibrosis. Comorbid lower airway inflammation such as bronchitis and asthma is often seen in SCUADs. In this review, we focus on two major eosinophilic inflammatory diseases in the upper airway, allergic rhinitis (AR) and chronic rhinosinusitis (CRS), and discuss their contribution to the pathophysiology of asthma, the representative counterpart in the lower airway.

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Allergic rhinitis and asthma

Pathological similarities and differences between AR and asthma

Upper and lower airways share common structures including ciliary epithelium, basement membrane, lamina propria, glands and goblet cells, the so called “United airways”.² Thus AR and asthma share pathological characteristics including the involvement of Th2-type cytokines such as IL-5, IL-13 and IL-31, eosinophilia-associated chemokines such as eotaxins, and cystenyl leukotrienes, which lead to pathological changes such as thickness of the basement membrane and goblet cell hyperplasia^{3–6} (Fig. 1). For example, we have shown that peripheral blood mononuclear cells (PBMCs) of two thirds of the patients with Japanese cedar/cypress pollinosis (JCCP) produced a substantial amount of IL-31 in response to pollen allergens, which was associated with the severity of the disease (Fig. 2).³ In addition, we also found that IL-31 induces MUC5AC gene expression in human airway epithelial cells.⁴ Furthermore, IL-31 was reported as a potential indicator in patients with allergic asthma; for example, IL-31 significantly induced vascular epithelial growth factor in human bronchial epithelial cells.⁵

On the other hand, differences between the upper and lower airways do exist. Thus, nasal mucosa attaches to bone whereas bronchial mucosa attaches to cartilage. Nasal mucosa is enriched with vessels whereas bronchial mucosa is enriched with smooth muscle cells. Thus the major cause of airway obstruction, especially in the early phase of the allergic response, is different; upper airway obstruction is caused by vascular dilation whereas lower airway obstruction arises from smooth muscle constriction (Fig. 2). In terms of remodeling, epithelial shedding is frequently seen in asthmatic bronchi but not in the nose of patients with AR.

Presence and characterization of comorbidity of allergic rhinitis and asthma

It is well-known that AR and asthma co-exist. In general, asthma occurs in 10–40% of patients with AR whereas AR occurs in 20–80%

of patients with asthma.^{7–13} Variation in the percentage with comorbidity may arise from differences in diagnostic criteria (e.g. questionnaire differences) and/or subjects sampled (e.g. age and time differences). For example, a recent cross-sectional nationwide survey in Japan called the SACRA study indicated that AR was present in 68.5% of asthmatic patients who used the self-administered questionnaire and in 66.2% of those who received the physician-administered questionnaire.¹³ Among patients with AR, those with poly-sensitization to inhaled allergens showed a tendency to have concomitant asthma as compared to mono-sensitized patients, and furthermore, sensitization to mites or cats induced comorbidity of asthma in mono-sensitized patients with AR.^{7,9}

The presence of concomitant AR can affect the severity of asthma in patients who have both diseases. Nasal condition is closely associated with the severity of the self-assessed asthma condition and with poor asthma control both in adults and children.^{14,15} A birth cohort study in the United Kingdom demonstrated that asthmatic children with AR were 2.89 fold more likely to experience frequent attacks of wheezing, 3.44 fold more likely to experience severe attacks of wheezing limiting speech, 10.14 fold more likely to have to frequently visit their doctor because of asthma, and 9 fold more likely to miss school as compared to those without AR.¹⁶ In addition, concomitant AR leads to a delay in the recovery of pulmonary function tests after asthma exacerbation in children.¹⁷ On the other hand, it is still debatable whether the presence of asthma affects the severity of AR according to the ARIA (allergic rhinitis and its impact on asthma) guidelines.^{8,9}

Effect of allergic rhinitis on lower airway inflammation and function

In the past, a “seesaw” phenomenon was proposed in which nasal symptoms were alleviated when asthma was exacerbated and vice versa in patients with coexisting rhinitis and asthma. However, it is currently suggested that the severity of AR and asthma is synchronized in general, and that the onset and/or exacerbation of AR leads to refractory asthma.^{18,19} For example, 35.1% of asthmatic patients suffering from JCCP showed an

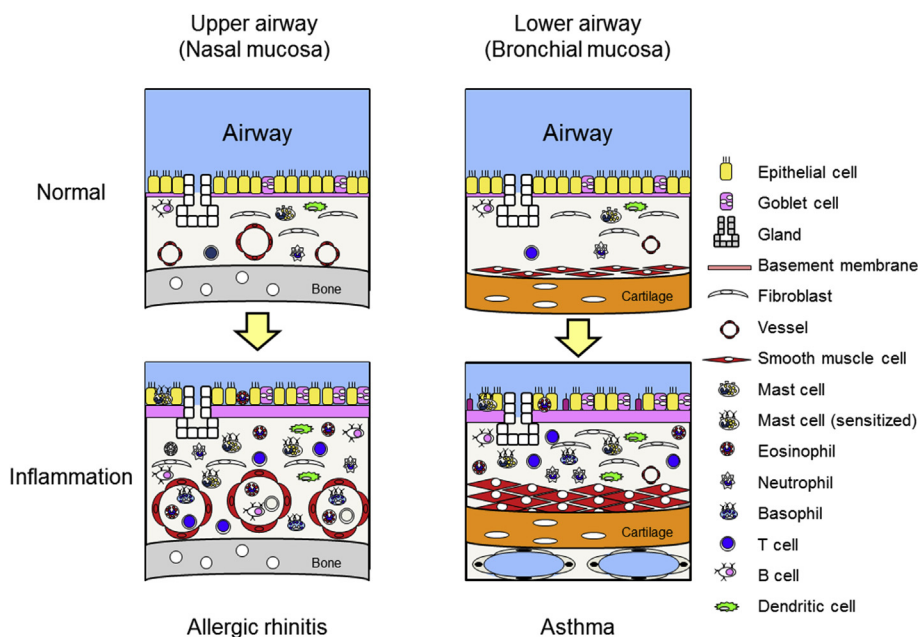


Fig. 1. Pathological similarities and differences between allergic upper and lower airway inflammation.

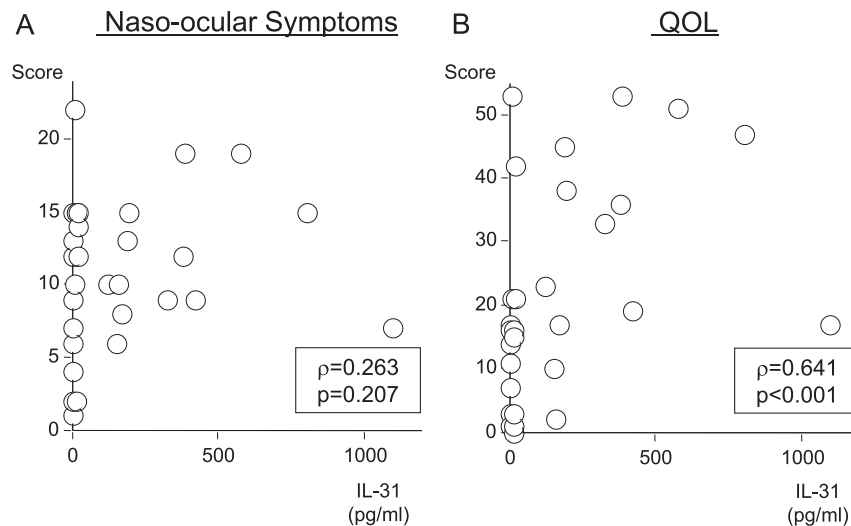


Fig. 2. Relationship between naso-ocular symptom score (A) and QOL (B) during the peak season of cypress pollen dispersion and the amount of IL-31 production by PBMCs in response to Cry j 1 (from Reference 3).

exacerbation of asthma symptoms including wheezing dyspnea, sputum and cough during the pollen dispersal season, and 31.7% of these patients showed a decrease in morning peak expiratory flow (PEF) of greater than 10% compared with the baseline values before pollen season.¹⁸

Hypersensitivity, obstruction and/or remodeling such as collagen deposition in the lower airways can be detected in patients with AR without awareness or diagnosis of asthma.^{20,21} Nasal provocation with allergens leads to tissue eosinophilia in bronchi and bronchial hyper-responsiveness to methacholine in non-asthmatic patients with AR alone.^{22,23} Such obstruction and hyper-sensitivity in lower airways is even seen in patients with recent onset of AR.²⁴ In addition, pollen exposure causes a significant elevation of exhaled nitric oxide in pollinosis patients without a diagnosis of asthma.²⁵

Several explanations have been proposed as to why the presence of AR induces inflammation and hyper-sensitivity of lower airways. These explanations include: 1) recruitment into lower airways of inflammatory cells activated by cytokines, chemokines and chemical mediators produced in the upper airway, 2) direct effect of cytokines and mediators on lower airways through the bloodstream, 3) naso-bronchial reflex and neurogenic inflammation, 4) aspiration of post-nasal drip containing inflammatory cells and mediators, and 5) nasal congestion-induced mouth breathing which causes dryness and cooling of the lower airways.^{23,26}

Effect of allergic rhinitis on the natural course of asthma

AR is a known risk factor for the new onset of wheeze and asthma. A survey revealed that development of new asthma was trebled in college students with AR that were followed for over 23 years as compared to those without rhinitis, and that this trend was more evident in those with perennial rhinitis.²⁷ Another longitudinal population-based survey showed that the 8.8-year cumulative incidence of asthma was 3.53 times higher in adult patients with AR as compared to healthy controls.²⁸ A similar risk is seen in pediatric AR. AR at the age of 7 years was associated with a significant increased risk of incident asthma in preadolescence, adolescence or adult life.²⁹ A birth cohort study in German children born in 1999 showed that AR up to the age of 5 years was a predictive factor for the development of wheezing between the ages of 5 and 13 years with an adjusted relative risk of 3.82.³⁰

Effect of intervention for allergic rhinitis on the natural course of asthma

As mentioned above, the onset of AR often precedes asthma both in children and in adults. It has therefore been investigated whether early intervention for AR can modify the natural course of asthma.

Allergen immunotherapy

Allergen immunotherapy is a curative treatment for AR which can induce remission without onset of IgE-mediated nasal symptoms.^{31–33} This treatment can modify the natural course of allergic diseases, the so-called “prevention effect”, which includes the prevention of new sensitization, of new onset of other allergic diseases and of relapse after termination of treatment.^{34–37} For example, a prospective open-labeled trial that investigated the long-term preventive effect of a 3-year course of subcutaneous immunotherapy (SCIT) in children with grass and/or pollen allergy showed that SCIT-treated children had significantly less asthma 7 years after termination of SCIT with an odds ratio of 2.5.³⁶ A placebo-controlled randomized 3-year study of sublingual immunotherapy (SLIT) with parietaria pollen vaccine for patients with AR demonstrated that SLIT showed a tendency to suppress the development of new onset of asthma as compared with the placebo treatment.³⁷

Pharmacotherapy

Pharmacotherapy for AR includes chemical mediator receptor antagonists such as antihistamines, anti-leukotrienes and anti-prostaglandin D2/thromboxane A2, chemical mediator release inhibitors such as disodium cromoglycate, Th2 cytokine inhibitors such as suplatast tosilate, and corticosteroids.³⁸ Among these therapies, anti-leukotrienes have an indication for both AR and asthma.^{38–40} A phase IV study demonstrated that montelukast is effective for both upper and lower airway symptoms in adult patients suffering from both asthma and AR.⁴¹ A similar effect was seen for intranasal corticosteroids and cromoglycate.^{42,43}

One randomized double-blind placebo-controlled study demonstrated that 18-months cetirizine treatment of pediatric patients with atopic dermatitis at the age of 1–2 years suppressed the new onset of asthma during the 18 months after termination of the pharmacotherapy, when the children were sensitized to mites

or pollens.⁴⁴ However, little is known as to whether pharmacotherapy for AR can modify the natural course of asthma. Initial (in other words, prophylactic or early interventional) treatment with antihistamines, anti-leukotrienes or intranasal corticosteroids before the start of continuous pollen dispersion is known to be effective for JCCP.^{38,45–47} Recently, Sagara et al. showed that initial treatment with pranlukast plus mequitazine significantly suppressed exacerbation airway hyper-responsiveness during the pollen season in non-asthmatic patients with JCCP.⁴⁸

Surgery

Surgery is one of the treatment options for severe cases of AR especially for those who suffer from oral breathing and/or intractable watery rhinorrhea.³⁸ Surgery includes degeneration surgery such as laser surgery, corrective surgery of the nasal cavity such as submucosal turbinectomy, and neurectomy of parasympathetic nerves such as posterior nerve neurectomy.⁴⁹ In patients with rhinitis concomitant with asthma, turbinate surgery improves not only the nasal symptoms but also asthma control.^{50,51} For example, argon plasma coagulation turbinectomy reduced the prevalence of patients with insufficient asthma control, as measured by the Asthma Control Test, from 79 to 4%, and this decrease was associated with diminished frequency of high nasal eosinophilia.⁵¹ However, to the best of our knowledge, there are no reports with high levels of evidence that support the possibility that nasal surgery might suppress the new onset of asthma in patients with AR.

Chronic rhinosinusitis and asthma

Pathological similarities and differences between chronic rhinosinusitis and asthma

CRS is one of the most common diseases.^{52,53} For example in the United States, the prevalence of CRS is 14%, and approximately 200,000 endoscopic sinus surgeries (ESS) for CRS are performed per year.⁵² CRS contains a variety of phenotypes and endotypes including CRS without nasal polyposis (CRSsNP), CRS with nasal polyposis (CRSwNP), fungal rhinosinusitis and odontogenic CRS.⁵⁴ Among these types, ECRS is histologically characterized by massive infiltration of eosinophils in the lamina propria, a thick basement membrane thickness, increased goblet cells, and epithelial shedding in sinonasal mucosa such as nasal polyps.⁵⁵ Similar immunological imbalances such as imbalances in cytokines and prostaglandins are seen in both ECRS and asthma (Fig. 3).^{56–60} Other molecules such as periostin appear to act as biomarkers that reflect the severity of both ECRS and asthma.^{61,62} Thus, ECRS can be regarded as “asthma of the upper airway”.¹ ECRS is the major endotype of CRSwNP in the United States and

Europe, and has been increasing in Asia.^{63,64} For example, there was a shift from predominantly neutrophilic to eosinophilic CRSwNP in Thai patients from 1999 to 2011.⁶³

Presence and characterization of comorbidity of chronic rhinosinusitis and asthma

It is well-known that CRS and asthma co-exist with a relationship similar to that between AR and asthma. In general, asthma occurs in 20–50% of patients with CRS. For example, a recent study showed that 23.1% of patients with CRS in Japan suffered from asthma.⁶⁵ Conversely, higher incidence of radiological abnormalities in paranasal sinuses was also seen in asthmatic patients.^{66–68} An early study showed that patients with mild-to-moderate asthma had an 88% incidence of abnormal sinus computed tomography (CT) findings, while patients with severe steroid-dependent asthma showed 100% abnormal sinus findings on CT-scans.⁶⁶ A later study also showed that increasing severity of asthma is associated with advancing radiological severity of CRS and a greater prevalence of allergic sensitization and nasal polypoidosis. However, a contradictory finding was also reported.^{67,68} Asthmatic patients with CRS showed a significant exacerbation of both generic and disease-specific QOL, and had significantly lower percentages of predicted forced expiratory volume in 1 s and percentage of predicted forced vital capacity than those without CRS.⁶⁹ In addition, poor outcome following ESS in CRS patients with concomitant asthma was shown in several studies.^{70,71}

Effect of chronic rhinosinusitis on lower airway inflammation and function

Lower airway inflammation and dysfunction has been seen in non-asthmatic patients with CRS. Approximately half of patients with CRS without the diagnosis of asthma showed a marked elevation in exhaled nitric oxide (>30 ppb).⁷² Similarly, approximately 70% of patients with CRS without the diagnosis of asthma showed a bronchial hyperresponsiveness (BHR) to methacholine.⁷³ A later study demonstrated that sneezing and a serum eosinophil count of over 300 cells per microliter may be predictive factors for BHR in patients with CRSwNP.⁷⁴ We compared pulmonary function between CRS patients without any diagnosed lung diseases and healthy subjects. There were no significant differences between the two groups in terms of forced expiratory volume in 1 s and the percentage of predicted vital capacity. However, the following parameters of pulmonary function were significantly affected in the CRS patients (compared with normal controls): percentage of predicted forced expiratory volume in 1 s; forced expiratory volume in 1 s/forced vital capacity ratio; PEF; mean forced expiratory

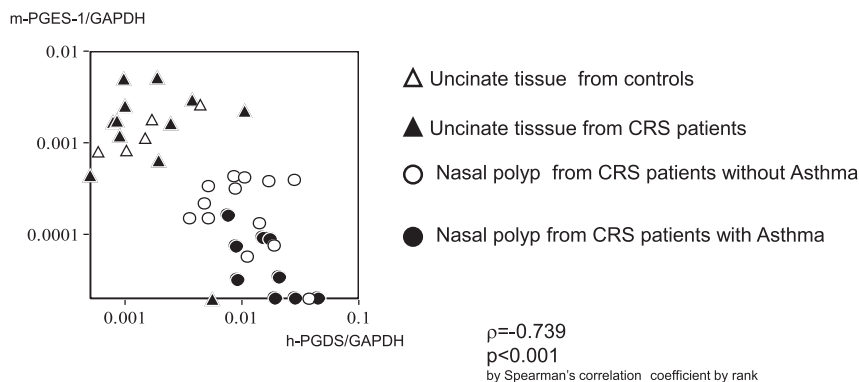


Fig. 3. Inverse relationship between PGD2 synthase (h-PGDS) and PGE2 synthase (m-PGES-1) mRNA levels in sinonasal tissues (from Reference 56).

flow between 25 and 75 per cent of the forced vital capacity; maximal expiratory flow rate at 50 per cent of vital capacity; maximal expiratory flow rate at 25 per cent of vital capacity; and maximal expiratory flow rate at 50 per cent of vital capacity/maximal expiratory flow rate at 25 per cent of vital capacity ratio (Fig. 4). In addition, the levels of IL-5 in nasal secretion in the middle meatus were significantly correlated with lung function changes.⁷⁵ We have also demonstrated in another study that obstructive lung dysfunction was more impaired in non-asthmatic patients with CRSwNP with peripheral blood eosinophilia (eosinophil percentage to total leukocyte equal or more than 5%) than in those without eosinophilia, especially in elderly patients aged 60 years old or more.⁷⁶

Similar explanations as those put forward to account for the relationship between AR and asthma have been proposed to explain why the presence of CRS induces lower airway inflammation and dysfunction.^{23,26} In particular, leukotrienes and cytokines produced in inflamed sinonasal mucosa seem to play a major role since urinary leukotriene excretion was significantly decreased after ESS.⁷⁷

Effect of intervention for chronic rhinosinusitis on asthma

Treatments for CRS differ among phenotypes.⁷⁸ In CRSsNP, pharmacotherapy including intranasal steroids (INS), mucolytic agents and/or long-term antibiotics such as 14-ring macrolides, and local manipulation such as nasal saline irrigation are first-line treatment options.^{53,79} For example, long-term combination therapy with S-carboxymethylcysteine and clarythromycin is effective for significantly improving subjective symptoms such as nasal discharge and post-nasal drip and objective findings such as CT scores in adult patients with CRS.⁷⁹ On the other hand, in CRSwNP especially ECRS, treatments that target the suppression of eosinophil activation and survival are considered as the first-line. These treatments include glucocorticoids (INS as a controller and systemic steroids as a reliever), anti-leukotrienes, anti-prostaglandin D2/thromboxane A2 and Th2 cytokine inhibitor.^{53,80,81} Since environmental microbes such as *Staphylococcus aureus* and fungi can evoke eosinophilia-associated cellular responses in sinonasal mucosa in patients with CRSwNP, nasal saline irrigation is also recommended.^{58,82,83} In terms of antibiotics, doxycycline showed a substantial effect on ECRS including on polyp size and ECP levels in nasal secretions whereas the effect of 14-ring macrolides on ECRS is

poor.^{81,84} Since biofilm is also known to be an intractable factor in the pathogenesis of CRS, the efficacy and safety of topical anti-biofilm agents such as surfactants and manuka honey have also been investigated.^{85,86} When the response to conservative treatments is poor, surgery for sinus ventilation and drainage is considered.

Pharmacotherapy

A few studies have demonstrated the efficacy of pharmacotherapy for CRS on lower airway symptoms and functions in CRS patients with asthma. Anti-leukotrienes show an anti-eosinophilic inflammatory effect in both upper and lower airways.^{39,87,88} A single-blinded, randomized, placebo-controlled trial demonstrated that, as compared with placebo, treatment with montelukast significantly improved nasal symptoms and inflammation such as eosinophilia in nasal smears as well as pulmonary symptoms and PEF in patients with CRSwNP concomitant with asthma.⁸⁹ On the other hand, little is known regarding whether INS is effective for lower airway inflammation and function in CRS patients. An open trial reported that symptoms and pulmonary function significantly improved after treatment with a combination of amoxicillin/clavulanate and fluticasone propionate aqueous nasal spray in poorly-controlled asthmatic children with CRS aged 5–12 years.⁹⁰ However, a short course of oral corticosteroid was also prescribed in that study.

The use of biologic agents such as anti-IgE and anti-IL-5 is a new strategy for the treatment of refractory CRS.⁹¹ Of these agents, treatment with omalizumab, a humanized anti-IgE monoclonal antibody, significantly improved both upper and lower airway pathophysiologies including nasal polyp size, radiological severity of CRS, nasal and asthma symptoms and QOL in patients with CRSwNP and asthma.⁹² Similar improvements were seen in those who are refractory to ESS (Fig. 5).

Surgery

In contrast to pharmacotherapy, the impact of sinus surgery on asthma has been demonstrated in a large number of studies. An earlier study showed an improvement in PEF 6 months after ESS ranging from 40 to 190 L/min in patients with CRS, especially ECRS, and with asthma.⁹³ A later study confirmed the effect, and found that medication for asthma could be reduced after surgery.⁷⁰ A more recent report showed an additional improvement in the use of bronchodilators, oral steroids and the need for hospitalization for

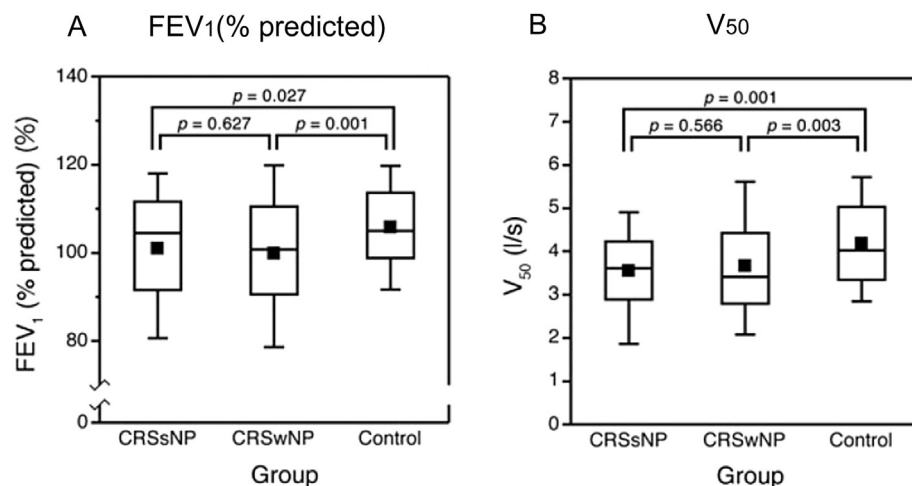


Fig. 4. Pulmonary function in patients with CRS and healthy controls. A: percentage of predicted forced expiratory volume in 1 s, and B: maximal expiratory flow rate at 50 percent of vital capacity.

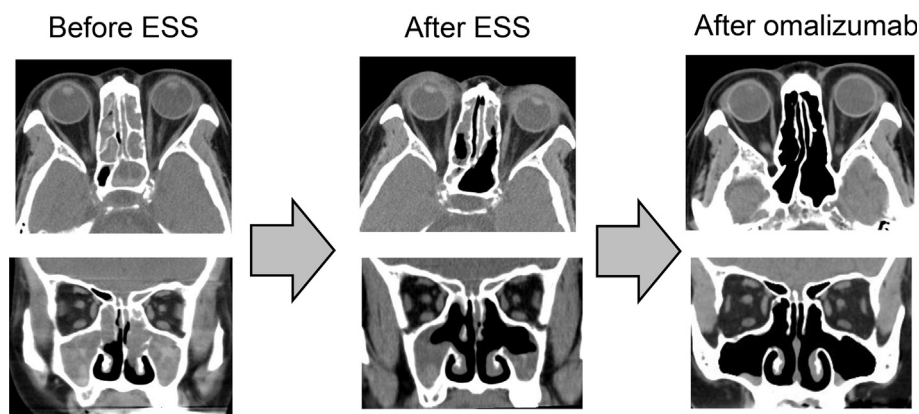


Fig. 5. Effect of omalizumab on refractory ECRS.

asthma.⁹⁴ Several mechanisms have been proposed to explain why sinus surgery improved asthma conditions. As mentioned above, urinary levels of LTE₄ were significantly higher in asthmatic patients, and the levels were significantly reduced following ESS.⁷⁷ This finding clearly suggests that sinus tissue may be a main organ for the production of LTs, and that control of upper airways including control by ESS provides a substantial benefit for asthma control. Reduced exhaled nitric oxide is also seen in asthmatic patients with CRS after ESS.^{95,96} In general, outcomes of CRS after treatment with ESS are worse in asthmatic patients as compared to non-asthmatics; however, based on the above information, ESS can be a treatment option for suppression of the severity of asthma.

Other treatments

Medical options other than the treatments described above include nasal decongestants in heavily congested CRS, antimycotics in fungal CRS, antireflux agents in gastro-esophageal reflux-associated CRS, and aspirin desensitization in aspirin-exacerbated respiratory disease (AERD)-associated CRS.^{77,97} Of these treatments, a beneficial effect of aspirin desensitization on both upper and lower airway symptoms has been noted in patients with AERD.⁹⁷ Recently, such an efficacy was confirmed in a randomized, double-blind, placebo-controlled study.⁹⁸ This study clearly demonstrated that 6 months oral aspirin desensitization after aspirin challenge leads to significant improvement in smell, reductions in sneezing and nasal congestion, improvement of asthma control, increase in peak nasal inspiratory flows, and reduction in the dosages of inhaled corticosteroids only in patients with aspirin-induced asthma but not in patients with aspirin-tolerant asthma. On the other hand, aspirin desensitization requires close monitoring for bronchospasm and dyspepsia.^{97,98}

Conclusions

The upper airways, especially the nose, act as a gatekeeper to control the physiology and pathology of the lower airways. In particular, AR and ECRS display a substantial impact on the symptoms and pulmonary function of asthma. Therefore, control of the united airway inflammation is crucial for improving the QOL of patients with co-existing AR/CRS and asthma. On the other hand, except for allergen immunotherapy for AR, little is known regarding whether early intervention for upper airway inflammation prevents the new onset of asthma. In addition, although some investigations suggest potent candidate genes that are associated with eosinophilic inflammation in both upper and lower airways, future investigations aimed at the detection of molecules that are

critical for the induction of eosinophilic united airway inflammation are warranted.^{99,100}

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Conflict of interest

The authors have no conflict of interest to declare.

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