—Original—

# One-Year Evaluation of Combined Treatment with an Intranasal Corticosteroid and Montelukast for Chronic Rhinosinusitis Associated with Asthma

Manabu Nonaka[1,2], Atsuko Sakanushi[1], Kaoru Kusama[1,2], Nozomu Ogihara[1,2] and Toshiaki Yagi[1]

[1]Department of Head & Neck and Sensory Organ Science, Graduate School of Medicine, Nippon Medical School
[2]Department of Otolaryngology, Nippon Medical School Tama Nagayama Hospital

**Abstract**

**Objectives:** Chronic rhinosinusitis associated with asthma is often difficult to treat effectively with intranasal corticosteroids alone. Thus, the aim of this study was to evaluate the effectiveness of combination treatment with an intranasal corticosteroid and a leukotriene-receptor antagonist (montelukast) in reducing the size of nasal polyps.

**Methods:** The subjects of this study were 20 patients with chronic rhinosinusitis associated with adult-onset asthma, which was being treated with inhaled corticosteroids. All patients were treated with intranasal fluticasone propionate, 200 μg/day, and montelukast, 10 mg/day, for 1 year. The size of nasal polyps and the score of sinus shadows were assessed with nasal endoscopy and computed tomography (CT), respectively, before and after treatment. The peripheral blood eosinophil counts were also evaluated before and after treatment.

**Results:** Nasal polyps were significantly smaller after both 6 months ($p<0.01$) and 12 months of treatment ($p<0.01$) than before treatment. The decrease in the shadow score was statistically significant after both 6 months ($p<0.01$) and 12 months of treatment ($p<0.01$). Significant reductions in peripheral blood eosinophil counts were also seen after both 6 months ($p<0.05$) and 12 months of treatment ($p<0.01$). A significant correlation was found between the rate of change in the peripheral blood eosinophil count and that in the CT score after both 6 months ($r=0.578$, $p=0.012$) and 12 months ($r=0.625$, $p=0.007$).

**Conclusion:** Combined treatment with intranasal fluticasone propionate and montelukast, for at least 1 year, is effective for chronic rhinosinusitis associated with adult-onset asthma.
(J Nippon Med Sch 2010; 77: 21–28)

**Key words:** chronic rhinosinusitis, eosinophils, intranasal corticosteroid, anti-leukotriene, asthma

Correspondence to Manabu Nonaka, Department of Otolaryngology, Nippon Medical School Tama Nagayama Hospital, 1–7–1 Nagayama, Tama, Tokyo 206–8512, Japan
E-mail: nonaka@nms.ac.jp
Journal Website (http://www.nms.ac.jp/jnms/)

## Introduction

Chronic rhinosinusitis, which is often associated with nasal polyps, is an airway inflammatory disease characterized by the accumulation of eosinophils and T lymphocytes and the development of epithelial metaplasia and stromal edema[1]. Accumulation of activated eosinophils is considered the hallmark of this disease[1]. Chronic rhinosinusitis is often associated with asthma. More than 50% of patients with sinus disease have asthma[2]. Eighty percent to 90% of adult patients with asthma have sinus abnormalities on computed tomography (CT)[3,4]. In patients with chronic rhinosinusitis associated with asthma, the severity of sinus abnormalities is reported to be related to sputum eosinophilia[4]. Experimentally induced sinonasal inflammation increases bronchial hyperresponsiveness and the number of eosinophils in the lower airways[5]. This association of chronic rhinosinusitis with asthma may reflect a shared pathogenesis of these conditions of the upper and lower airways. As with asthma, chronic rhinosinusitis is also associated with the local production of helper T type 2 cytokines, such as interleukin (IL)-5, and eosinophil-attracting chemokines, such as eotaxin.

The circulating eosinophil count is often increased in chronic rhinosinusitis associated with asthma[3,4], and it has been reported that eosinophilic infiltration of the paranasal sinus mucosa is often present when the circulating eosinophil count is increased[6]. A significant positive correlation has been shown between the CT scores in patients with rhinosinusitis and the peripheral blood eosinophil counts in patients with mild-to-moderate asthma[3] or severe asthma[3,4]. Thus, the peripheral eosinophil count may reflect the severity of chronic rhinosinusitis associated with asthma.

Intranasal corticosteroids can be used as a long-term therapy for nasal polyposis. Some degree of efficacy has been reported for 80% of patients with nasal polyposis treated with an intranasal corticosteroid[7]. However, when intranasal corticosteroids are ineffective, systemic corticosteroids are recommended. Systemic corticosteroid treatment is more effective than intranasal corticosteroids for chronic rhinosinusitis associated with asthma but is only used on a short-term basis due possible side effects[8].

Leukotrienes (LTs), which are derivatives of arachidonic acid, are generated in allergic rhinitis as well as in asthma. It has been reported that chronic hyperplastic eosinophilic sinusitis is characterized by increased levels of cysteinyl LTs (CysLTs) which are associated with asthma and are correlated with the peripheral blood eosinophil count[6]. In addition, CysLT1 receptor expression has been reported to be upregulated in nasal polyps from patients with aspirin-sensitive rhinosinusitis[9]. Ragab et al.[10] have reported the efficacy of montelukast, a LT-receptor antagonist, in the treatment of nasal polyposis associated with asthma. Given its efficacy and low rate of side effects in the treatment of allergic airway inflammation, montelukast may be useful for the long-term treatment of chronic rhinosinusitis associated with asthma.

The present study was designed to evaluate the efficacy of combined treatment with intranasal fluticasone propionate (FP) and montelukast for chronic rhinosinusitis associated with asthma being controlled with inhaled corticosteroids. The efficacy was evaluated on the basis of the reduction in the size of nasal polyps, the score of sinus shadows as assessed with CT, and the peripheral blood eosinophil count.

## Materials and Methods

### Patients

Twenty patients with chronic rhinosinusitis and adult-onset asthma were enrolled in this study. Capsulated hydrophobic carrier polymer-radioallergosorbent tests (CAP-RASTs) for serum IgE specific for 9 common aeroallergens were performed in all patients. All patients had a history of nasal obstruction, rhinorrhea, postnasal dripping, episodic dyspnea, and wheezing and a documented reversibility in hyperresponsiveness to inhaled histamine. All patients were nonsmokers and were being treated with an inhaled corticosteroid (FP, 200–400 μg/day, in 18 patients; budesonide, 400 μg/

Table 1 Classification of polyp size

| |
|---|
| Polyp size was rated on a four-point scale: |
| 0: No polyps |
| 1: Small-sized polyps (not reaching the lower edge of the middle turbinate) |
| 2: Intermediate polyps (extending between the upper and lower edges of the inferior turbinate) |
| 3: Large polyps (extending below the lower edge of the inferior turbinate) |

day, in 2 patients); 7 patients were also being treated with inhaled salmeterol xinafoate (50 μg/day), and 5 patients were also being treated with theophylline (400 mg/day p.o.) for more than 1 year. None of the patients had been treated with an anti-LT agent or with an intranasal corticosteroid for at least 3 month before this study. All patients were examined and treated by the same physician for the duration of the study and visited the hospital at least once a month. At each visit, compliance with prescribed medications was confirmed. All patients had given written informed consent, and the study protocol was approved by the Ethics Committee of the Nippon Medical School Hospital.

### Design

At entry, the patient and disease characteristics were documented with a structured questionnaire. The age at onset of asthma was determined, and the type of asthma and the medications for asthma were evaluated. Then a blood sample was taken, and nasal endoscopy was performed. On a separate day, standardized CT scanning of the paranasal sinuses was performed. After that, combined treatment with intranasal FP (200 μg/day) and montelukast (10 mg/day) was started and continued for 1 year. All baseline medications were continued. The blood tests, endoscopic evaluation of nasal polyps, and CT scanning were performed every 6 months.

### Nasal Endoscopy and CT Scanning of the Nasal Sinuses

Nasal endoscopy was used to measure the size of nasal polyps at each visit. Polyp size was rated on a 4-point scale (**Table 1**). Sinus CT scanning was performed, and the scans were analyzed for evidence of shadows in the sinuses and osteomeatal complexes. A CT-scan score was assigned, as previously described by Lund and Mackay[11]. Briefly, the CT shadow of each sinus (maxillary, frontal, anterior ethmoidal, posterior ethmoidal, and sphenoidal sinuses) was assigned a score of 0, no abnormality; 1, partial opacification; or 2, total opacification. The osteomeatal complexes were scored as 0 (unobstructed) or 2 (obstructed). Each side was considered separately. The maximum possible total score was 24 points (20 points from the sinuses and 4 points from the osteomeatal complexes). The sinus CT scans were reviewed by one of the authors, who was experienced in interpreting sinus CT scans and was blinded regarding each patient's history and examinations.

### Statistical Analysis

For statistical analysis, Wilcoxon's signed rank test and the Mann-Whitney U test were used for paired and nonpaired comparisons, respectively. Correlations between the improvement rates of the peripheral blood eosinophil count and of the CT score were analyzed with Spearman's rank correlation test.

## Results

### Patient Characteristics

The clinical data of the 20 patients are summarized in **Table 2**. Nine patients had allergy, and 11 patients did not have allergy, as indicated by at least two positive CAP-RASTs. Of the 20 patients, 8 were judged on the basis of their history to have aspirin-sensitive asthma, and 3 had allergy. Twelve patients did not have aspirin-sensitive asthma. During this study 2 patients had asthma attacks, which were treated with hydrocortisone, 400 mg/day, for 2 days. Each of these attacks occurred more than 3 months before the postadministration determinations of the three assessed variables (peripheral blood eosinophils, nasal polyp score, and

Table 2 Patient characteristics

| | |
|---|---|
| Number | 20 (11 males, 9 females) |
| Age (yr) | 55.6 ± 12.6 |
| Allergic status | 9 allergic, 11 non-allergic |
| Aspirin idiosyncrasy | 8 aspirin-sensitive, 12 not aspirin-sensitive |
| Peripheral blood eosinophil counts (/μL) | 748.9 ± 328.7 |

The results are expressed as the mean ± SD unless otherwise indicated.

Table 3 Comparison of CT scores among sinuses and before and after treatment

| | before treatment | after treatment | |
|---|---|---|---|
| | | 6 M | 12 M |
| Maxillary sinus | 2.2 ± 1.2 ** | 1.4 ± 1.3 §§ | 1.6 ± 1.4 § |
| Frontal sinus | 2.5 ± 1.6 * | 2.0 ± 1.7 § | 1.8 ± 1.7 § |
| Ethmoid sinus | | | |
| Anterior | 3.2 ± 0.8 | 2.6 ± 1.0 § | 2.5 ± 1.1 §§ |
| Posterior | 3.2 ± 1.1 | 2.3 ± 1.5 § | 2.4 ± 1.5 § |
| Sphenoid sinus | 2.2 ± 1.7 ** | 1.3 ± 1.7 § | 1.4 ± 1.7 § |

Comparisons of scores for the maxillary, frontal and sphenoid sinuses with the scores for the anterior and posterior ethmoid sinuses were performed with the Mann-Whitney U test: * P<0.05; ** P<0.01.
Pretreatment and posttreatment scores were compared by means of Wilcoxon's rank signed test: §P<0.05; §§P<0.01.
Results are expressed as the mean ± SD.

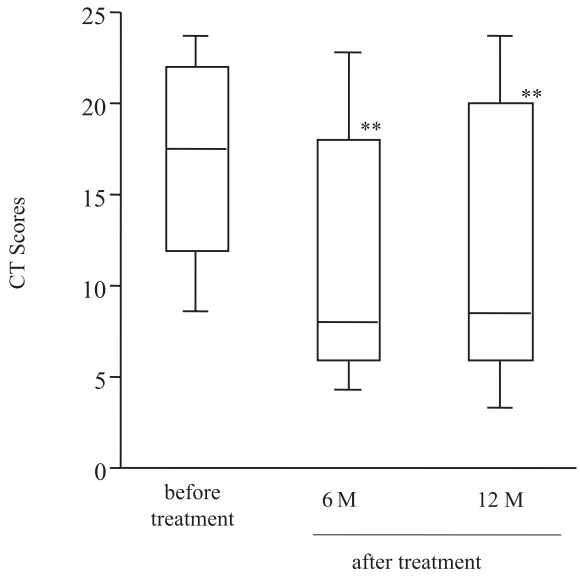


Fig. 1 Effects of the treatment on the total CT scores.
Box plots show the median values with 25% and 75% interquartiles; the error bars represent the 10th and 90th percentiles. **P<0.01 compared with CT scores before treatment.

CT score). The CT scores and nasal polyp scores of these two patients did not change during this study.

**Sinus CT Scan**

Before treatment, the CT scores for shadows in the anterior and posterior ethmoid sinuses were higher than the scores for the maxillary sinus (both p<0.01), sphenoid sinus (both p<0.01), and frontal sinus (both p<0.05) (**Table 3**). All 20 patients had sinus CT scan abnormalities. The total CT shadow scores were lower after 6 months (p<0.01) and 12 months (p<0.01) (**Fig. 1**) of treatment with intranasal FP and montelukast. The CT shadow scores had decreased in each of the sinuses after 6 and 12 months (**Table 3**).

**Size of Nasal Polyps**

The changes in the total nasal polyp scores are shown in **Figure 2**. The polyp size score after 6 months of treatment was clearly lower than that before treatment (p<0.01). A decrease in the nasal polyp score was also seen with the continuation of treatment and after 12 months of treatment (p<0.01). No difference in the nasal polyp score was found

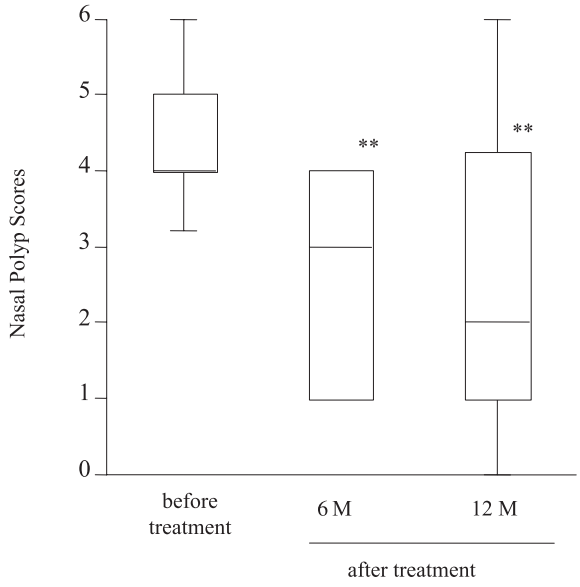


Fig. 2 Effects of treatment on nasal polyp scores. Box plots show the median values with 25% and 75% interquartiles; the error bars represent the 10th and 90th percentiles. **P<0.01 compared with nasal polyp scores before treatment.

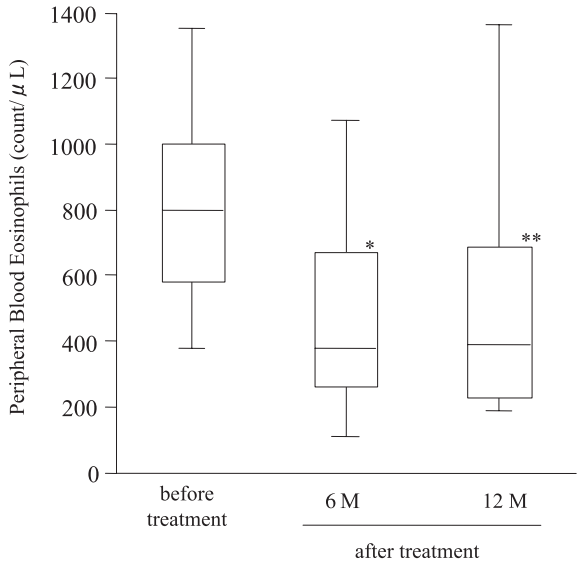


Fig. 3 Effects of the treatment on peripheral blood eosinophils.
Box plots show the median values with 25% and 75% interquartiles; the error bars represent the 10th and 90th percentiles. *P< 0.05 at 6 months and **P<0.01 at 12 months compared with peripheral blood eosinophils before treatment.

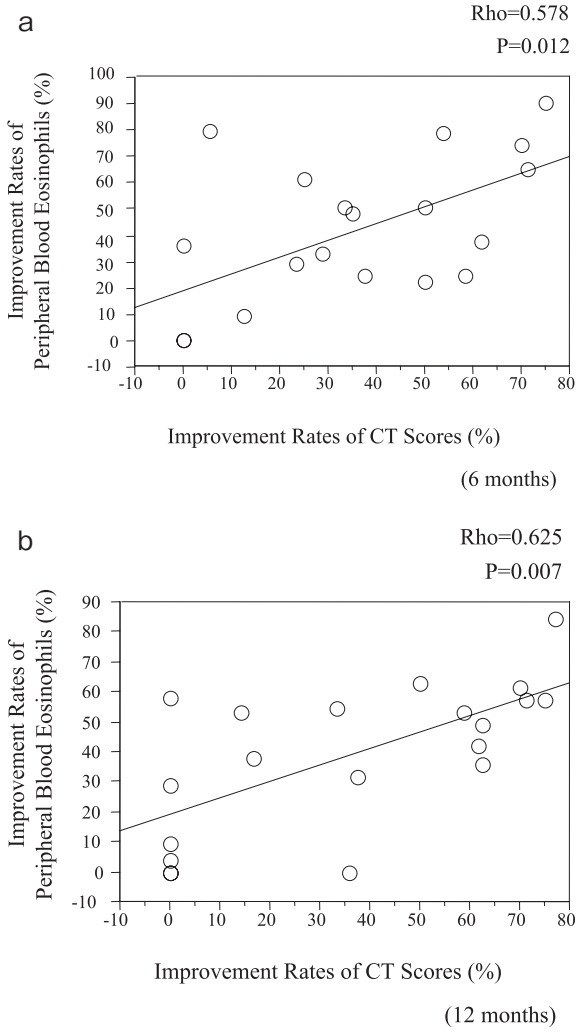


Fig. 4 Relationships between the improvement rates for peripheral blood eosinophil counts and CT scores after 6 months of treatment (a) and 12 months of treatment (b).

between 6 months and 12 months.

**Peripheral Blood Eosinophils**

The peripheral blood eosinophil count after 6 months of treatment was lower than that before treatment ($p<0.05$). A decrease was also seen after 12 months of treatment ($p<0.01$; **Fig. 3**).

**Correlations between Results**

The posttreatment rates of change in the peripheral blood eosinophil count after 6 months of treatment and 12 months of treatment were calculated relative to the pretreatment count. The improvement rates for the CT scores after 6 months and 12 months of treatment were similarly calculated. A significant correlation was found

between the improvement rates of the peripheral blood eosinophil count and the CT score at 6 months (r=0.578, p=0.012) and at 12 months (r=0.625, p=0.007) (**Fig. 4**).

## Discussion

This study was designed to evaluate the efficacy of a combination treatment of an intranasal corticosteroid with an LT-receptor antagonist for chronic rhinosinusitis associated with asthma. The results confirm the efficacy of combined intranasal FP and montelukast therapy in reducing the size of nasal polyps and sinus shadows (assessed with CT for 1 year) in the treatment of chronic rhinosinusitis associated with adult-onset asthma being controlled with inhaled corticosteroids. This study also demonstrates that circulating eosinophils are significantly reduced after co-administration of intranasal FP and montelukast. Moreover, the greater was the decrease in circulating eosinophils, the greater was the decrease in sinus shadows.

Intranasal corticosteroids are recognized as being highly effective in the treatment of nasal polyposis[7]. Intranasal corticosteroids reduce polyp size, increase the nasal peak-flow index, and decrease nasal symptoms[7]. Moreover, intranasal corticosteroids cause almost no adverse effects and can be administered on a long-term basis. For these reasons, intranasal corticosteroid treatment is widely advocated for the control of nasal polyposis, but the response to this treatment is often only partial. van Camp and Clement[8] used oral corticosteroids to treat 25 patients with massive nasal polyposis and found that 72% of the patients showed subjective improvement due to involution of polyps in the nasal cavity immediately after treatment. However, within 5 months there was a strong tendency for nasal polyps to recur, and two patients had major side effects, i.e., diabetes and a stomach ulcer. Combined (local and systemic) corticosteroid therapy has been reported to be highly effective during short-term treatment[12]. Thus, repeated systemic treatment with corticosteroids is often necessary for control of nasal polyposis for 3 years by means of combined corticosteroid therapy[13].

Although various chemical mediators are released during airway inflammation, evidence strongly suggests that the C4, D4, and E4 CysLTs play key roles in asthma. LTs are at least 1,000 times more potent as bronchoconstrictors than histamine or methacholine. In addition, CysLTs are known to be chemotactic for eosinophils and to promote adhesion-molecule expression, inhibit eosinophil apoptosis, and increase microvascular leakage and mucus secretion. Steinke et al.[6] have examined the presence of CysLTs in nasal polyp tissues obtained from patients with chronic hypertrophic sinusitis. They found that CysLT concentrations were much higher in nasal polyp tissues obtained from patients with eosinophilic sinusitis, which is closely associated with blood eosinophilia and asthma, than in nasal polyp tissues from patients with noneosinophilic sinusitis. Sousa et al.[9] have reported that in nasal polyp tissues from patients with aspirin-sensitive rhinosinusitis the expression of the CysLT1 receptor, but not of the LTB4 receptor, is upregulated. Recent evidence has shown that 3 months of treatment with montelukast reduces the size of nasal polyps in patients with chronic rhinosinusitis associated with asthma[10]. Considering that montelukast causes minimal side effects, it may be, in addition to topical corticosteroids, useful for the long-term treatment of chronic rhinosinusitis associated with asthma.

It has been shown that intranasal corticosteroids reduce eosinophilia in nasal polyps[14], perhaps due to a reduction of eosinophil influx or a shortening of eosinophil survival. A reduction in endothelial adhesion molecules, such as P-selectin, may contribute to reduced eosinophil adhesion to endothelial cells in nasal polyps, and reductions in IL-4 and IL-13, which are strong inducers of eosinophil-attracting chemokines, such as eotaxin, may lead to reduced eosinophil infiltration[14]. Reduced eosinophil survival could occur due to both a direct apoptosis-inducing effect of corticosteroids and an indirect effect through suppression of IL-5 in nasal polyps[15]. It has been reported that in chronic airway inflammation, such as in rhinosinusitis and asthma, locally produced growth factors, such as IL-5, can regulate peripheral blood eosinophils, basophils, and their progenitors[16]. A reduction in these growth

factors by topical corticosteroids may cause eosinophil suppression in the peripheral blood[16].

In studies in patients with asthma, corticosteroids have not demonstrated inhibitory effects on the production of CysLTs[17]. Specifically, CysLTs can be detected in the airways of patients with asthma despite high-dose oral corticosteroid therapy. The presence of CysLTs can be explained, in part, by the fact that corticosteroids do not affect mast cell release of CysLTs *in vivo* in humans. The complementary action of LT-receptor antagonists with corticosteroids at mucosal sites for the treatment of asthma has been documented[18].

We have shown that combined therapy with an intranasal corticosteroid and montelukast decreased the peripheral blood eosinophil count for 1 year. The eosinophils are believed to be important effector inflammatory cells in chronic rhinosinusitis associated with asthma. Decreased peripheral blood eosinophil counts have previously been reported with LT-receptor antagonists[19] and inhaled corticosteroids[16]. Inhaled corticosteroids also decrease the number of airway eosinophils[16]. It has been documented that topical corticosteroids can decrease local hemopoietic factors, such as IL-5 and granulocyte-macrophage colony-stimulating factor, leading to reduced counts of peripheral blood eosinophils, basophils, and their progenitors[16]. Meanwhile, LT-receptor antagonists may retard bone marrow eosinophil maturation by inhibiting the synergistic effects of CysLTs and peptide growth factors on eosinophil/basophil stem cell maturation[20].

Our data have clearly shown that sinus shadows, assessed with CT, were reduced after combined treatment with an intranasal corticosteroid and montelukast and that the reduction was maintained for at least 1 year. The treatment was effective in all sinuses. Moreover, the decreases in peripheral blood eosinophil count after 6 months and 12 months of treatment were correlated with decreases in CT scores. Considering that intranasal corticosteroids cannot reach all of the sinuses directly, the efficacy seen in all sinuses and the correlations between the decreases in peripheral blood eosinophil counts and in sinus shadows were thought to be results of both the local and systemic effects of combined therapy.

The results of this study show that combined therapy with an intranasal corticosteroid and montelukast is effective for decreasing the size of nasal polyps and decreasing CT findings in patients with chronic rhinosinusitis associated with asthma and also show that these favorable effects are maintained for at least 1 year. Considering that both drugs cause few side effects, this combined therapy for chronic rhinosinusitis associated with asthma may be more effective than other treatments, which must often be continued for a longer time.

**Acknowledgment:** The authors wish to express their deep gratitude to Ms. S. Saito for her invaluable technical assistance.

## References

1. Nguyen LH, Fakhri S, Frenkiel S, Hamid QA: Molecular immunology and immunotherapy for chronic sinusitis. Curr Allergy Asthma Rep 2003; 3: 505–512.
2. Leynaert B, Neukirch F, Demoly P, Bousquet J: Epidemiologic evidence for asthma and rhinitis comorbidity. J Allergy Clin Immunol 2000; 106: S201–205.
3. Bresciani M, Paradis L, Des Roches A, et al.: Rhinosinusitis in severe asthma. J Allergy Clin Immunol 2001; 107: 73–80.
4. ten Brinke A, Grootendorst DC, Schmidt JT, et al.: Chronic sinusitis in severe asthma is related to sputum eosinophilia. J Allergy Clin Immunol 2002; 109: 621–626.
5. Braunstahl GJ, Overbeek SE, Kleinjan A, Prins JB, Hoogsteden HC, Fokkens WJ: Nasal allergen provocation induces adhesion molecule expression and tissue eosinophilia in upper and lower airways. J Allergy Clin Immunol 2001; 107: 469–476.
6. Steinke JW, Bradley D, Arango P, et al.: Cysteinyl leukotriene expression in chronic hyperplastic sinusitis-nasal polyposis:importance to eosinophilia and asthma. J Allergy Clin Immunol 2003; 111: 342–349.
7. Lildholdt T, Rundcrantz H, Lindqvist N: Efficacy of topical corticosteroid powder for nasal polyps:a double-blind, placebo-controlled study of budesonide. Clin Otolaryngol Allied Sci 1995; 20: 26–30.
8. van Camp C, Clement PA: Results of oral steroid treatment in nasal polyposis. Rhinology 1994; 32: 5–9.
9. Sousa AR, Parikh A, Scadding G, Corrigan CJ, Lee TH: Leukotriene-receptor expression on nasal mucosal inflammatory cells in aspirin-sensitive rhinosinusitis. N Engl J Med 2002; 347: 1493–1499.
10. Ragab S, Parikh A, Darby YC, Scadding GK: An open audit of montelukast, a leukotriene receptor antagonist, in nasal polyposis associated with asthma. Clin Exp Allergy 2001; 31: 1385–1391.

11. Lund VJ, Mackay IS: Staging in rhinosinusitus. Rhinology 1993; 31: 183–184.
12. Tuncer U, Soylu L, Aydogan B, Karakus F, Akcali C: The effectiveness of steroid treatment in nasal polyposis. Auris Nasus Larynx 2003; 30: 263–268.
13. Bonfils P, Norès JM, Halimi P, Avan P: Corticosteroid treatment in nasal polyposis with a three-year follow-up period. Laryngoscope 2003; 113: 683–687.
14. Hamilos DL, Thawley SE, Kramper MA, Kamil A, Hamid QA: Effect of intranasal fluticasone on cellular infiltration, endothelial adhesion molecule expression, and proinflammatory cytokine mRNA in nasal polyp disease. J Allergy Clin Immunol 1999; 103: 79–87.
15. Adachi T, Motojima S, Hirata A, et al.: Eosinophil apoptosis caused by theophylline, glucocorticoids, and macrolides after stimulation with IL-5. J Allergy Clin Immunol 1996; 98: S207–215.
16. Gibson PG, Dolovich J, Girgis-Gabardo A, et al.: The inflammatory response in asthma exacerbation: changes in circulating eosinophils, basophils and their progenitors. Clin Exp Allergy 1990; 20: 661–668.
17. Dworski R, Fitzgerald GA, Oates JA, Sheller JR: Effect of oral prednisone on airway inflammatory mediators in atopic asthma. Am J Respir Crit Care Med 1994; 149: 953–959.
18. Laviolette M, Malmstrom K, Lu S, et al.: Montelukast added to inhaled beclomethasone in treatment of asthma. Montelukast/Beclomethasone Additivity Group. Am J Respir Crit Care Med 1999; 160: 1862–1868.
19. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB: Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. Arch Intern Med 1998; 158: 1213–1220.
20. Wickremasinghe RG, Khan MA, Hoffbrand AV: Do leukotrienes play a role in the regulation of proliferation of normal and leukemic hemopoietic cells? Prostaglandins Leukot Essent Fatty Acids 1993; 48: 123–126.

(Received, August 3, 2009)
(Accepted, August 31, 2009)