*The Laryngoscope*


# Efficacy of Leukotriene Antagonists as Concomitant Therapy in Allergic Rhinitis

Cemal Cingi, MD; Kivanc Gunhan, MD; Linda Gage-White, MD, PhD, FAAOA; Halis Unlu, MD

**Objectives/Hypothesis:** The symptoms of allergic rhinitis result from an immunoglobulin E-dependent mast cell activation cascade, marked by the release of inflammatory mediators, including histamine. Patients with perennial allergic rhinitis also have elevated levels of cysteinyl leukotrienes (CysLTs) in nasal lavage fluid. Histamine and CysLTs produce different responses in the pathogenesis of allergic rhinitis, and this study tested the hypothesis that the effects of combined antihistamine and leukotriene antagonist therapy would be more effective than antihistamine alone.

**Study Design:** Multicentered, prospective, randomized, placebo-controlled, parallel-group.

**Methods:** Three groups totaling 275 patients using: 1) fexofenadine alone, 2) fexofenadine with montelukast, or 3) fexofenadine with placebo, participated in a 21-day trial conducted during the spring pollen season. Objective analysis included pre- and poststudy physical examination findings and nasal resistance measurements. Subjective data gathered included a daily patient diary and pre- and poststudy patient satisfaction measurements.

**Results:** The group using both fexofenadine and montelukast showed significantly better control of nasal congestion both subjectively, using patient diary and visual analog scale evaluations, and objectively, using rhinomanometry and physical examination, compared to groups using antihistamine alone or with placebo.

**Conclusions:** Our data provided both objective and subjective evidence that leukotriene receptor antagonist-antihistamine combination therapy is more effective than antihistamine alone in the control of allergic rhinitis symptoms.

**Key Words:** Allergic rhinitis, leukotrienes, montelukast, leukotriene receptor antagonist.

**Level of Evidence:** 1a

***Laryngoscope*, 120:1718–1723, 2010**

## INTRODUCTION

Allergic rhinitis is a globally common chronic inflammatory condition with an increasing prevalence, causing a sociologic and economic burden. The symptoms of allergic rhinitis result from a specific immunoglobulin E-dependent mast cell activation, the release of inflammatory mediators, the subsequent recruitment and activation of leukocyte populations, and the presence of a predominant Th2-type cytokine profile that are all triggered by exposure of the nasal mucosa to airborne allergens. These symptoms, which include nasal congestion, itching, sneezing, and rhinorrhea, are associated with substantial morbidity, primarily in the context of reduced quality of life and productivity.

The initiation and regulation of allergic inflammation provides rich cellular sources of various mediators such as histamine and cysteinyl leukotrienes (CysLTs), which play important roles in the pathogenesis of allergic airway inflammation.[1] Leukotrienes and histamine are quantitatively the most prominent mediators in the final pathways of allergic rhinitis.

Cysteinyl leukotrienes ($LTC_4$, $LTD_4$, and $LTE_4$) promote a variety of proinflammatory actions, including microvascular leakage, inflammatory cell chemotaxis (particularly eosinophils), mucus hypersecretion, and neuronal stimulation, all of which are relevant to the pathophysiology of allergic rhinitis.[2]

Recent evidence suggests the involvement of CysLTs in the pathophysiology of allergic rhinitis. It shows that: 1) CysLTs are released from inflammatory cells that participate in allergic rhinitis,[3] 2) receptors for CysLTs are located in nasal tissue,[4] 3) CysLTs are increased in patients with allergic rhinitis and are released following allergen exposure,[5] 4) nasal administration of CysLTs reproduces the symptoms of allergic rhinitis,[2] 5) CysLTs play roles in the maturation and

From the Department of Otorhinolaryngology and Head-Neck Surgery, Osmangazi University, Eskisehir, Turkey (C.C.); Department of Otorhinolaryngology and Head-Neck Surgery, Celal Bayar University, Manisa, Turkey (K.G., H.U.), and Departments of Otolaryngology and Pediatrics, Health Sciences Center, Louisiana State University, Shreveport, Louisiana (L.G.-W.), U.S.A.

Editor's Note: This Manuscript was accepted for publication on February 1, 2010.

Presented at the American Academy of Otolaryngic Allergy Annual Meeting, San Diego, California, U.S.A., October 1–3, 2009.

The authors have no funding, financial relationships, or conflicts of interest to disclose.

Send correspondence to Linda Gage-White, MD, PhD, 2627 Fairfield Ave., Shreveport, LA 71104. E-mail: lgagewhite@yahoo.com

**DOI: 10.1002/lary.20941**

tissue recruitment of inflammatory cells,[6] 6) a complex inter-regulation between CysLTs and a variety of other inflammatory mediators exists, 7) CysLTs increase nasal vascular permeability and blood flow, inducing plasma protein exudation and leading to blockage and mucus secretion,[7] and 8) levels of CysLTs rise in ragweed-sensitive patients during ragweed season.[5]

There are many treatments available for allergic rhinitis, but current guidelines state that oral antihistamines are first-line therapy[8] with intranasal corticosteroids. Intranasal corticosteroids are effective as first-line treatment in moderate and severe disease and are used traditionally to combat nasal congestion and the other symptoms associated with allergic rhinitis, but corticosteroids do not inhibit the release of leukotrienes in humans in vivo.[9] Moreover, their usage is limited by their long-term potential side effects, which occur in about 5% of patients. There has also been some concern over their effect on growth in children.

Because histamine is a key mediator of the symptoms of allergic rhinitis, antihistamines assume first priority in controlling the resulting symptoms, particularly as they have a rapid onset and can be used as needed by the patients. Second generation antihistamines, like fexofenadine, do not cross the blood brain barrier and as a result are especially attractive to patients because they do not cause clinically relevant sedation. Although there are a few studies illustrating a beneficial effect of newer antihistamines on nasal blockage, generally these drugs, as a class, are less effective against nasal congestion and blockage than against sneezing and itching.[10]

Since the introduction of cysteinyl-leukotriene receptor antagonists (LTRA), initially as a medication for allergic lower airway disease, evidence regarding their effectiveness in allergic upper airway disease has been increasing. Montelukast, an LTRA and an antiasthmatic drug, was recently approved for clinical use in the treatment of allergic rhinitis through clinical studies performed in children and adults.[11]

Histamine and CysLTs have different roles in the pathogenesis of allergic rhinitis, and it therefore seems logical to expect that the effects of combined antihistamine and antileukotriene therapy would be more effective than either treatment alone. Although several publications report the mostly subjective effectiveness of LTRA in the treatment of allergic rhinitis, the results are inconsistent and few studies used objective parameters, such as rhinomanometry, in their assessment.[12]

We hypothesized that fexofenadine alone would not completely reduce nasal congestion (as objectively measured by total nasal resistance), and that the addition of montelukast to antihistamine medication would reduce both the early and late phase responses, providing a synergistic effect by targeting the second of the two important mediators inducing this response. Therefore, the objective of this trial was to measure any synergistic effect of LTRA medication when combined with antihistamine in treating patients with seasonal allergic rhinitis, as measured by objective, subjective, and quality-of-life parameters.

## MATERIALS AND METHODS

### *Study Design*

This multicentered, prospective, randomized, placebo-controlled, parallel-group (three treatment groups) trial was conducted during the spring pollen season. The study design included three visits. At visit one, researchers recorded initial clinical findings and evaluations, and determined patients' eligibility for the study. At visit two, patients were randomly allocated to receive fexofenadine 120 mg/day (group 1), fexofenadine 120 mg/day with montelukast 10 mg/day (group 2), or fexofenadine 120 mg with placebo (group 3), and were given the coded medication (group 1 received one bottle, whereas groups 2 and 3 each received two bottles) and a daily rhinitis diary. To increase compliance, the patients filled out the initial diary entry during this visit with their physicians in order to establish baseline information and to explain to them how to fill out the forms. The third and final visit occurred at the end of 21 days of medication, when physicians re-examined the patients and collected the patients' evaluations and medication bottles. The physicians who assessed the patients (C.C., K.G.) were blinded to the patient's treatment group. Previous studies showed the effects of both fexofenadine and montelukast occurred within 21 days, so this interval was chosen to reveal maximum effects without being too difficult for patients to complete.

Patients were to take the study medication once daily in the morning, irrespective of food consumption. Medication bottle contents were counted at trial completion to evaluate compliance. Tablet counts confirmed that all patients had at least 90% compliance.

The appropriate institutional review board approved the protocol and informed consent forms. All patients gave their written informed consent. No pharmaceutical companies funded the study or contributed to the study design, outcome evaluation, or writing of this article.

### *Patients*

Subjects (ages 15 to 68 years) who had a documented clinical history of seasonal allergic rhinitis for at least 1 year with a positive skin test to grass and/or tree pollens and who were otherwise in good health were eligible for the study. The study excluded otherwise-eligible patients if, before the commencement of the study, they: 1) had been treated with study drugs or decongestants within 1 week, 2) had been treated with astemizole within 2 months, 3) had been treated with topical, oral, or parenteral corticosteroids within 1 month, or 4) had received immunotherapy within 3 years. Patients with asthma, severe concurrent disease, deviated nasal septum, turbinate hypertrophy, nasal polyposis, or concomitant sinonasal disorders were also excluded from the study.

### *Outcome Measures*

***Physical findings.*** Physicians documented each patient's physical findings at the first and third visits. Inferior turbinate color was classified as natural (0), pale (1), bluish (2), or severely pale or bluish (3). Edema, nasal discharge, and congestion were ranked as none (0), mild (1), moderate (2), or severe (3).

***Nasal resistance.*** Nasal airflow was objectively measured by active anterior rhinomanometry (SRE 2000; RhinoMetrics, Lynge, Denmark). The procedure included the placement of a pressure sensor in one nostril and an air flow detector in the other nostril. Hence, the resistance of each nasal cavity and total nasal airway resistance could be calculated

TABLE I.
Patient Baseline Characteristics.

| | Treatment Groups | | |
|---|---|---|---|
| | FEX | FEX + MNT | FEX + Placebo |
| No. patients | 106 | 112 | 57 |
| No. men (%) | 43 (41) | 46 (41) | 26 (45) |
| Age, yr (mean ± SD) | 30.7 ± 7.1 | 29.7 ± 6.7 | 30.2 ± 5.5 |
| House type A (%)* | 67 (63.2) | 71 (62.3) | 39 (68.4) |

*House type A is an apartment in the city, and house type B is a house in a suburb/rural area.

FEX = Fexofenadine; MNT = montelukast; SD = standard deviation.

separately. Nasal airflow was reported as the sum of recorded airflow through the right and left nostrils in milliliters per second at a pressure difference of 150 Pa across the nasal passage ($Pa/cm^3/s$). Each patient had a minimum of four airflow measurements, and the mean was recorded once reproducible values were achieved.

***Daily rhinitis diary card.*** On a daily diary card, the patients evaluated and recorded their allergic rhinitis symptoms on a four-point scale (0 to 3). After the initial instruction and data recording at the second visit, patients evaluated and graded their symptoms and kept diaries for 21 days. The questions rated nasal symptoms (stuffy, itchy nose, sneezing, and runny nose) as: severe symptoms, very disturbing some of the time and/or disturbing most of the time (0); moderate symptoms, noticeable and disturbing some of the time (1); mild symptoms, noticeable but not bothersome (2); or symptoms not noticeable (3). Similar four-point scales have shown validity in previous allergic rhinitis trials.[10]

### *Satisfaction evaluation*

The patients' satisfaction with their relief of symptoms was also graded by a visual analog scale (VAS) from 0 to 100 (0 = much worse, 100 = much better) in the daily diary and at the end of the medication period.

### *Efficacy evaluation*

All patients evaluated the efficacy of the medication used through a VAS of 0 to 100 at the conclusion of the trial (0 = much worse, 100 = much better). At the last visit (visit 3), patient and physician completed global evaluations by responding to the question, "Compared to when I (the patient) entered the study, my (the patient's) overall nose and non-nose symptoms are now," using a seven-point scale of 0 being very much better and 6 being very much worse. Similar global evaluations have been used in other recent asthma and allergic rhinitis trials.

### *Statistical Analysis*

SPSS for Windows 15.0 (SPSS Inc., Chicago, IL) was used in analyzing the data. The distribution of variables was checked initially by the Shapiro-Wilk test. Parametric tests were applied to data showing normal distribution, and nonparametric tests were applied to data showing abnormal distribution. The $\chi^2$ test was used to compare the baseline distributions of sex and house types of each treatment group. Comparison of age distribution of groups was done by using independent samples $t$ test. The difference analysis of the diary scores kept by each group was compared by repeated measures analysis of variance. In addition, the Bonferroni test was applied for checking the reliability of differences among the groups.

The initial symptom scores for nasal discharge, sneezing, nasal congestion, and itching of patients were compared with the Mann-Whitney $U$ test. Variations in these symptoms and physical findings during the treatment period were compared by the Wilcoxon signed rank test.

Independent samples $t$ test was used to compare the efficacy and satisfaction evaluation scores of the groups.

## RESULTS

### *Patients*

For the 275 patients enrolled in the study, the baseline characteristics were similar across treatment groups (Table I). There were no significant differences in sex and age distributions of the groups ($P > .05$). The distribution of patients' residential environments (house types) was also not statistically different ($P > .05$) among the groups.

***Physical findings.*** Although the groups were assigned randomly, there was no significant difference in mean baseline values at day 0 of physical findings or symptoms in all three groups ($P > .05$). Figure 1 shows the initial and day 21 evaluation of inferior turbinate color.

Figure 2 shows similar initial values for turbinate edema, nasal discharge, and congestion in all three groups. Nasal endoscopic examination at day 21 showed: 1) a significant additional effect on turbinate edema with combination therapy in group 2 ($P = .045$), 2) no significant difference in nasal discharge among the groups ($P > .05$), and 3) a significant difference in group 2 for nasal congestion when compared to group 1 ($P < .001$) and group 3 ($P < .001$).

***Nasal resistance.*** Rhinomanometrically, total nasal resistance decreased on average from 0.42 $Pa/cm^3/s$ to 0.32 $Pa/cm^3/s$ with fexofenadine alone, and from 0.43 $Pa/cm^3/s$ to 0.33 $Pa/cm^3/s$ with fexofenadine and placebo therapy. Neither change was statistically significant ($P > .05$). Fexofenadine plus montelukast combination therapy (group 2) resulted in a statistically significant average decline from 0.43 $Pa/cm^3/s$ to 0.27 $Pa/cm^3/s$ ($P = .027$). The value at day 21 for group 2 was also statistically different when compared to day 21 in groups 1 and 3 ($P = .038$) (Fig. 3).

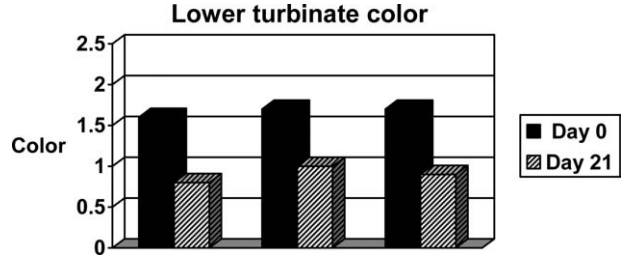


Fig. 1. Inferior turbinate color was classified as natural (0), pale (1), bluish (2), and severely pale or bluish (3).

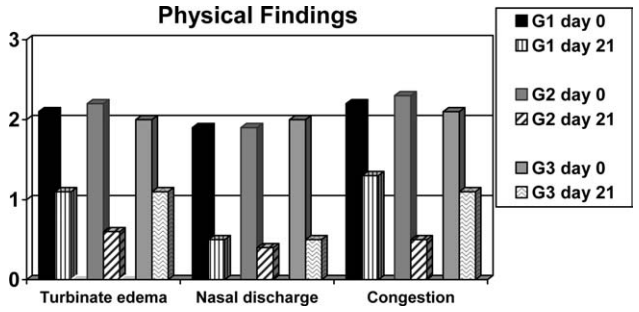


Fig. 2. Physical findings via endoscopic examination. 0 = none, 1 = mild, 2 = moderate, 3 = severe. G = group.

### *Symptom Measures*

***Daily rhinitis diary card.*** Mean symptom scores for nasal congestion, nasal itching, sneezing, and rhinorrhea showed an initial improvement after the first 3 days in all groups. Group 2 improved more than the other groups, and the differences became statistically significant after the 9th, 10th, 11th, and 13th days for nasal congestion ($P = .003$), itching ($P = .009$), sneezing ($P = .004$), and rhinorrhea ($P = .001$), respectively (Fig. 4). On day 21, nasal congestion scores were significantly better only in group 2 with the fexofenadine/montelukast medication.

The overall wellness score also increased in a similar way in the first 7 days in all groups, but only combination therapy scored significantly better results at the end of 21 days. Baseline and final scores of all groups were statistically significantly improved for nasal congestion, itching, sneezing, and rhinorrhea.

***Efficacy evaluation.*** The patients' evaluation of the efficacy of the medication used revealed that group 2 scored significantly better than groups 1 and 3 ($P = .037$). The difference was analyzed using SigmaStat software (Aspire Software International, Ashburn, VA). Similar results were observed in global satisfaction ($P = .029$) when compared with the fexofenadine only and fexofenadine plus placebo groups. Figure 5 shows the satisfaction results.

## DISCUSSION

Antihistamines are the first-line treatment for allergic rhinitis. They are traditionally effective for a large range of symptoms like rhinorrhea, sneezing, itchy nose, irritation, and ocular symptoms, but are less effective on nasal congestion. LTRAs have been studied as both add-on medications or alone for allergic rhinitis treatment.[11]

LTRAs have been shown to inhibit rhinitis symptoms after experimental nasal allergen challenge and in naturally occurring exposures. Interestingly, in some cases the range of symptoms inhibited by LTRA in an allergen challenge is greater than the range of symptoms produced by direct administration of leukotrienes to the nose. This suggests that leukotrienes might produce some symptoms by action at sites not affected by direct nasal administration of leukotrienes, or that stimulated leukotrienes might interact with other mediators released at the same time to produce these symptoms.

Nasal administration of leukotrienes in nonatopic individuals increases nasal blood flow in Doppler studies, while having no effect on itching, sneezing, and discharge, unlike challenges with antigen or histamine. Furthermore, leukotriene $D_4$ exhibits approximately 5,000-fold more potency than histamine on a microgram basis when administered topically intranasally.[2] It causes vascular engorgement, resulting in nasal congestion and increased nasal airway resistance, but does not produce secretions, itching, or sneezing.[13] Besides being more potent in producing nasal congestion than histamine, the symptoms CysLTs produce are more prolonged.[13] One would predict, then, that blocking these local effects would help relieve nasal congestion.

Nasal obstruction is a prominent symptom in most patients with allergic rhinitis. It is the most bothersome

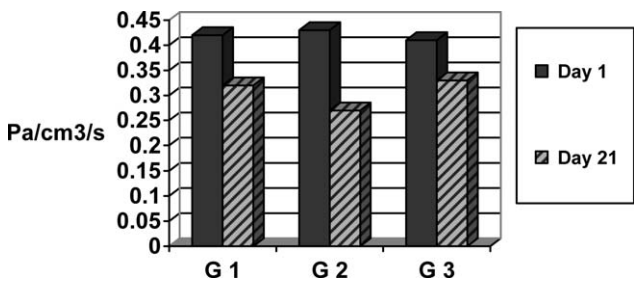


Fig. 3. Nasal resistance via active anterior rhinomanometry. G = group.

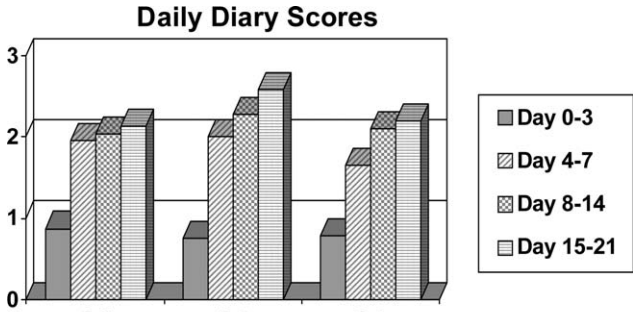


Fig. 4. Scores from daily rhinitis diary card (average of nasal congestion, itching, sneezing, and rhinorrhea). 0 = severe, 1 = moderate, 2 = mild, 3 = natural.

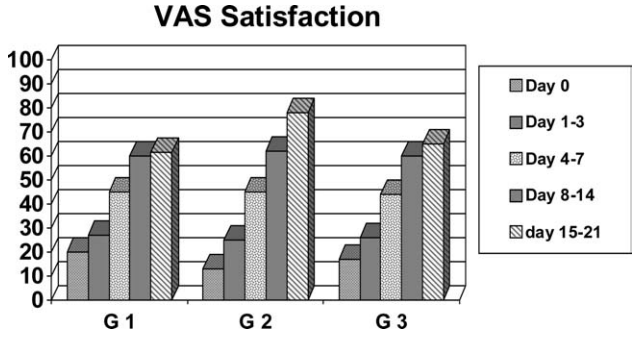


Fig. 5. Comparison of average values of satisfaction evaluation via visual analog scale (VAS).

and most difficult to control symptom of allergic rhinitis and is due to pooling of blood in the cavernous sinusoids, which produces a subsequent reduction in the airway lumen in response to allergic stimulation.

Anterior rhinomanometry is a well-defined laboratory tool that measures function in terms of nasal resistance. In many studies, determination of the degree of nasal obstruction is mainly based on the patient's subjective self assessment. The accuracy and the reliability of such descriptions are questionable. In studies dealing with nasal airway obstruction in patients with seasonal allergic rhinitis after a nasal provocation test, a marked sensation of nasal congestion would be expected, as the change in nasal patency occurs acutely. Consequently, subjective grading of nasal congestion by patients might be fundamentally skewed. Nasal airflow and resistance measurements represent an objective and quantitative assessment of nasal patency, and anterior rhinomanometry is the most reliable method to assess these parameters.[14]

In this study, the rhinomanometric values were obtained according to the international committee report on standardization of rhinomanometry. Our data demonstrate that fexofenadine, alone or combined with placebo, decreased total nasal resistance, but this decline did not reach statistical significance by the end of the 21 days of medication. In contrast, fexofenadine combined with montelukast reduced the total nasal resistance significantly, and also provided superior control of nasal congestion. This effect was also observed as a reduction of turbinate congestion by physical examination (same physician for day 1 and 21).

Some of the second generation antihistamines control nasal congestion. Fexofenadine was found to be more effective than desloratadine in the management of symptoms of seasonal allergic rhinitis, including nasal congestion.[15] The approved dosage of fexofenadine in the United States is 180 mg once daily or 60 mg twice daily; and in Europe, Latin America, and Australia is 120 mg once daily or 60 mg twice daily. Previous studies demonstrated that fexofenadine 120 mg once daily and fexofenadine 180 mg once daily have equal efficacy in relieving the symptoms of allergic rhinitis.[10] The data obtained from our study showed some effect with fexofenadine 120 mg (alone or with placebo) in reducing nasal congestion but did not reach statistical significance. However, concomitant use of LTRA with fexofenedine 120 mg led to a statistically significant improvement.

In this study, the subjective patient satisfaction in all groups was similar until the 10th day of medication. The difference in efficacy became significant after the 10th day. This confirms prior studies showing LTRA alone or with antihistamine combination medication was not found very effective for the first week in some of the earlier reported studies.[11] In this study, concomitant use of LTRA with fexofenedine led to a statistically significant improvement in wellness scores after the first week, as measured by both the average daily diary scores and quality-of-life measurements (i.e., efficacy and satisfaction evaluations). Our study was held in spring, with patients documented to be allergic to spring pollens via skin prick test. The combination of LTRA and antihistamine was significantly more effective than antihistamine plus placebo or antihistamine alone. Histamine challenge induces neurologic responses, such as sneezing and itching, but does not reproduce all symptoms of allergic rhinitis, suggesting the involvement of other mediators like CysLTs.[7] Both antihistamines and LTRAs have antiallergic and anti-inflammatory properties, including differing effects on mediator release and chemoattraction of inflammatory cells. This explains why the combination of antihistamine with montelukast provides an additive effect compared with antihistamine alone.

## CONCLUSION

These data provide both an objective and subjective basis for the use of LTRA-antihistamine combination therapy in the control of allergic rhinitis. The control of nasal congestion with the combined dosage was significantly improved both subjectively (using two different measures) and objectively (by rhinomanometry and physical examination) compared to antihistamine alone or with placebo. The effect is likely due to the additional anti-inflammatory activity provided by the reduction of inflammatory infiltrate and cytokine levels.

More studies are needed to fully evaluate the long term clinical effectiveness of LTRA, especially as concomitant therapy, but our data suggest it is reasonable and safe to use the combination of these agents as standard therapy for patients with allergic rhinitis with congestion.

## BIBLIOGRAPHY


1. Peters-Golden M, Sampson AP. Cysteinyl leukotriene interactions with other mediators and with glucocorticosteroids during airway inflammation. *J Allergy Clin Immunol* 2003;111:537–542.
2. Bisgaard H, Olsson P, Bende M. Effect of leukotriene D4 on nasal mucosal blood flow, nasal airway resistance and nasal secretion in humans. *Clin Allergy* 1986;16:289–297.
3. Figueroa DJ, Borish L, Baramki D, Philip G, Austin CP, Evans JF. Expression of cysteinyl leukotriene synthetic and signalling proteins in inflammatory cells in active seasonal allergic rhinitis. *Clin Exp Allergy* 2003;33: 1380–1388.
4. Shirasaki H, Kanaizumi E, Watanabe K, et al. Expression and localization of the cysteinyl leukotriene 1 receptor in human nasal mucosa. *Clin Exp Allergy* 2002;32: 1007–1012.
5. Volovitz B, Osur SL, Bernstein JM, Ogra PL. Leukotriene C4 release in upper respiratory mucosa during natural exposure to ragweed in ragweed-sensitive children. *J Allergy Clin Immunol* 1988;82:414–418.
6. Busse W, Kraft M. Cysteinyl leukotrienes in allergic inflammation: strategic target for therapy. *Chest* 2005;127: 1312–1326.
7. Howarth PH, Salagean M, Dokic D. Allergic rhinitis: not purely a histamine-related disease. *Allergy* 2000;55:7–16.
8. Bousquet J, Van Cauwenberge P, Khaltaev N; ARIA Workshop Group; World Health Organization. Allergic rhinitis and its impact on asthma. *J Allergy Clin Immunol* 2001; 108 (suppl 5):S147–S334.
9. Sebaldt RJ, Sheller JR, Oates JA, Roberts LJ, Fitzgerald GA. Inhibition of eicosanoid biosynthesis by glucocorticoids

in humans. *Proc Natl Acad Sci U S A* 1990;87: 6974–6978.
10. Howarth PH, Stern MA, Roi L, Reynolds R, Bousquet J. Double-blind, placebo-controlled study comparing the efficacy and safety of fexofenadine hydrochloride (120 and 180 mg once daily) and cetirizine in seasonal allergic rhinitis. *J Allergy Clin Immunol* 1999;104:927–933.
11. Philip G, Malmstrom K, Hampel FC Jr, et al. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002;32:1020–1028.
12. Topuz B, Ogmen GG. Montelukast as an adjuvant to mainstay therapies in patients with seasonal allergic rhinitis. *Clin Exp Allergy* 2003;33:823–826.
13. Okuda M, Watase T, Mezawa A, Liu C. The role of leukotriene D4 in allergic rhinitis. *Ann Allergy* 1988;60:537–540.
14. Lund VJ. Objective assessment of nasal obstruction. *Otolaryngol Clin North Am* 1989;22:279–290.
15. Berger WE, Lumry WR, Meltzer EO, Pearlman DS. Efficacy of desloratadine, 5 mg, compared with fexofenadine, 180 mg, in patients with symptomatic seasonal allergic rhinitis. *Allergy Asthma Proc* 2006;27:214–223.