

Comparison of a nasal glucocorticoid, antileukotriene, and a combination of antileukotriene and antihistamine in the treatment of seasonal allergic rhinitis

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Asthma, rhinitis,
other respiratory
diseases

Background: Allergic rhinitis requires active intervention for symptom relief. A combination of antileukotriene and antihistamine drugs has been suggested to provide additive treatment benefits for patients with allergic rhinitis.

Objective: We evaluated how such a combination treatment would affect symptoms and local mucosal eosinophilia in comparison with a nasal glucocorticoid.

Methods: In a double-blind, randomized study 62 patients with grass pollen-induced allergic rhinitis received a nasal glucocorticoid (fluticasone propionate aqueous nasal spray [FPANS], 200 µg/d), an antileukotriene (montelukast, 10 mg/d), a combination of montelukast with an antihistamine (loratadine, 10 mg/d), or placebo throughout the season. Cromoglycate eyedrops and a limited amount of loratadine were allowed as rescue medication for severe symptoms. Patients recorded their symptoms for nasal blockage, itching, rhinorrhea, and sneezing. Before and during the season, nasal biopsy specimens were obtained from patients for evaluation of local eosinophilic inflammation.

Results: During the peak season, both FPANS and combined montelukast-loratadine were significantly more effective than placebo and montelukast alone for daytime symptom prevention. For nighttime symptoms, FPANS was significantly more effective compared with all other treatments, whereas combined montelukast-loratadine and montelukast alone did not provide significant symptom prevention compared with placebo. The pollen-induced increase in the numbers of epithelial eosinophils was significantly lower for FPANS-treated patients compared with that seen in all other treatment groups.

Conclusion: In patients with seasonal allergic rhinitis, intranasal glucocorticoids are more effective than an antileukotriene drug or combined antileukotriene-antihistamine for the reduction of pollen-induced nasal eosinophilic inflammation and for control of nasal symptoms. (*J Allergy Clin Immunol* 2002;109:949-55.)

Key words: Allergic rhinitis, glucocorticoids, antileukotriene, antihistamine, mucosal inflammation

Allergic rhinitis is a common disease, affecting people primarily during the most productive period of life and thereby imposing a major economic effect.^{1,2} Although not life-threatening, allergic rhinitis presents a significant discomfort to the patient and requires active intervention during symptom periods. Two of the most widely used pharmacologic treatments of allergic rhinitis to date, nasal glucocorticoids and oral antihistamines, became available several decades ago. Although the safety profile and efficacy of these drugs have been significantly improved, no new class of pharmacologic treatment has been introduced for management of allergic rhinitis during the last quarter of a century.

Numerous mediators are implicated in the pathogenesis of allergic rhinitis, 2 of the most abundant being histamine and cysteinyl leukotrienes. Specific antagonists are available that influence both of these mediators, but the effect of antileukotrienes has been documented mainly for treatment of asthma only. In patients with allergic rhinitis, a leukotriene receptor antagonist, zafirlukast, had a moderate effect on the acute rhinitis symptoms in a "day-in-the-park" study.³ However, treatment with zafirlukast over the pollen season proved to be significantly less effective compared with treatment with a nasal glucocorticoid, beclomethasone dipropionate, in reduction of pollen-induced allergic rhinitis symptoms.⁴ Similarly, antihistamines are known to provide less symptom relief compared with that provided by nasal glucocorticoids.⁵⁻⁷

The effect of intranasal administration of histamine and cysteinyl leukotrienes on allergic rhinitis symptoms is quite characteristic. Histamine has been suggested to be primarily involved in the induction of sneezing, rhinorrhea, and nasal itching, but it has an obstructive effect only at relatively high concentrations.⁸ On the other hand, intranasal administration of leukotrienes causes mainly nasal blockage only, with very limited effects on the 3 other characteristic symptoms of allergic rhinitis.⁹⁻¹¹ Thus the combination of these 2 antimediator therapies could theoretically provide additional benefits compared with the blockage of a single mediator only. This was also suggested by a recent study on the treatment of allergic rhinitis with concomitant administration of an antileukotriene, montelukast, and an antihistamine, loratadine, demonstrating significantly better symptom

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Abbreviation used

FPANS: Fluticasone propionate aqueous nasal spray

relief compared with the modest improvement of rhinitis symptomatology with each of the treatments alone.¹² Such an additional beneficial effect was, however, not reported in a subsequent larger study.¹³ Also, in asthmatic patients a combination of montelukast and loratadine given for 2 weeks provided significantly better symptom control compared with that provided by montelukast alone.¹⁴ The effect of such a combination treatment needs to be compared with the most efficient and safest treatment of allergic rhinitis to date (ie, nasally administered glucocorticoids), however, to evaluate the clinical implications of these observations.

We therefore designed a study to compare the effect of an oral antileukotriene, montelukast; a combination of montelukast and an antihistamine, loratadine; and a nasal glucocorticoid, fluticasone propionate aqueous nasal spray (FPANS), on the symptoms of allergic rhinitis during a naturally occurring pollen season. Also, we evaluated the effect of these drugs on the development of local eosinophilic inflammation in the nasal mucosa.

METHODS

The study was approved by Ethics Review Committee of Clinical Research Studies of the University of Tartu, and all patients provided written informed consent.

Study design

The study had a randomized, double-blind, double-dummy, parallel-group, placebo-controlled design and was conducted between March and August 1999. The study design consisted of 5 patient visits. Visit 1 was a prestudy visit for assessment of each patient's eligibility for the study. At visit 2, patients received record cards for recording their daily nasal symptoms and provided preseason nasal biopsy samples, venous blood samples for hematology and serum biochemistry assessment, and samples for urinalysis. At visit 3, patients were provided with one of the following treatments, according to a computer-generated allocation schedule: group A, active FPANS, 50 µg per actuation, 2 actuations per nostril per day plus placebo capsules for montelukast and loratadine; group B, active montelukast, 10 mg/d plus placebo nasal spray plus placebo capsules for loratadine; group C, active montelukast, 10 mg/d, plus active loratadine, 10 mg/d plus placebo nasal spray; and group D, placebo for all 3 arms. Patients were instructed to start treatment on the same predetermined date approximately 2 to 3 weeks before the expected beginning of the grass pollen season. All treatment was administered once a day in the morning and lasted for a total of 50 days, covering the whole pollen season. For rescue medication, patients were provided with cromoglycate eyedrops and a limited amount of additional loratadine tablets, and patients were instructed to record any use of rescue medication in the daily record cards. At visit 4, during the peak of the grass pollen season, patients provided the second, in-season nasal biopsy sample. Visit 5 was a follow-up visit performed approximately 1 month after the end of the treatment and the grass pollen season.

Starting from visit 2 and throughout the treatment period, patients were instructed to record their symptoms for nasal blockage, sneezing, rhinorrhea, and nasal itching in the record cards separately for nighttime and daytime by using a score of 0 to 4. The fol-

lowing scoring system was used for nasal blockage: 0, breathing through the nose freely and easily; 1, slight difficulty breathing through the nose; 2, moderate difficulty breathing through the nose; 3, severe difficulty breathing through the nose; and 4, breathing through the nose is very difficult or impossible. For sneezing, rhinorrhea, and nasal itching, scores of 0 to 4 indicated no, mild, moderate, severe, and very severe symptoms, respectively.

Patients

Patients of both sexes aged between 15 and 50 years with a known history of allergic rhinitis during the grass pollen season for at least the 2 previous years were considered eligible for the study. Allergy to grass pollen was confirmed at visit 1 by means of a positive skin prick test response to the mixture of grass pollen allergens, as well as to 3 locally common grass pollen extracts (*Phleum pratense*, *Lolium perenne*, and *Festuca pratensis*; ALK, Hørsholm, Denmark) separately. A positive skin prick test response against tree pollens, which pollinate earlier in the year, was considered an exclusion criterion. Other exclusion criteria included perennial rhinitis, concurrent purulent nasal infection, use of steroids in any form during the course of the study, or the presence of any serious or unstable concurrent disease. Female patients were eligible for the study only if they demonstrated a negative pregnancy test result.

Originally, 67 patients (37 male and 30 female patients) were recruited into the study. However, between prestudy visit 1 and visit 2, 3 patients withdrew consent, 1 patient was excluded for not fulfilling criteria for age, and another patient was excluded for use of nasal glucocorticoids. Thus 62 patients (36 male and 26 female patients; age range, 15-49 years; mean age, 29.2 years) were randomized to treatment and subsequently used as the intent-to-treat population for statistical analysis.

Pollen count measurement

Grass pollen counts in the study area during the season of 1999 were measured daily with a Burkard volumetric pollen trap (Burkard Manufacturing Co, Ltd, Rickmansworth, United Kingdom).

Immunohistochemistry for EG2⁺ eosinophils

At visits 2 (preseason samples) and 4 (in-season samples), all patients provided nasal biopsy specimens for evaluation of eosinophilic inflammation in nasal mucosa. Biopsy specimens were taken, processed, and stained for EG2⁺ eosinophils, as previously described.⁴ For staining, we used mouse monoclonal anti-human EG2 antibody (Kabi Pharmacia Diagnostics AB, Uppsala, Sweden), followed by incubation with horseradish peroxidase-conjugated sheep F(ab')₂ anti-mouse immunoglobulins (Amersham International plc, Little Chalfont, United Kingdom). Species- and isotype-matched immunoglobulins (mouse IgG1; Sigma Chemical Co, St Louis, Mo) were used instead of the primary antibody to control specificity of the staining.

Numbers of EG2⁺-stained cells were counted in a blinded fashion with a light microscope (Axioplan 2; Carl Zeiss Jena GmbH, Jena, Germany) at 400× magnification separately for epithelium and within 200 µm of the subepithelium. The area of epithelium and the respective area of the subepithelium was measured with an image-analysis system (KS 400; Kontron Elektronik GmbH, Echting, Germany), and the number of positively stained cells per square millimeter was calculated. Data are expressed as the change of EG2⁺ cells from the preseason samples to the in-season samples.

Data analysis

The intent-to-treat population, consisting of all subjects who were randomized to treatment and who received at least one dose of study medication, was used for statistical analysis.

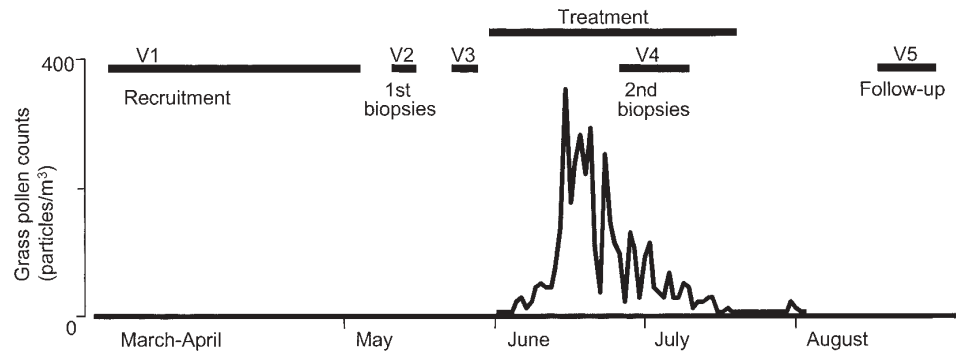


FIG 1. Study design and grass pollen counts in the study area.

TABLE I. Baseline demographic characteristics of patients

	Sex (M/F)	Age, mean $\pm$ SD (y)	Duration of rhinitis (% ≤ 5 years/% > 5 years)
FPANS (n = 13)	7/6	28.4 $\pm$ 6.4	8/92
Montelukast (n = 16)	10/6	28.3 $\pm$ 8.0	25/75
Montelukast-loratadine (n = 15)	6/9	30.1 $\pm$ 9.9	20/80
Placebo (n = 18)	13/5	29.8 $\pm$ 10.4	22/78

The primary endpoint in the study was the patient's recorded nasal symptom score. A Wilcoxon signed-rank test was performed to evaluate whether the pollen season had an overall effect on nasal symptoms in patients with allergic rhinitis, comparing the mean of the symptoms during the run-in period of 2 weeks before initiation of treatment with in-season symptoms. Comparisons between treatment groups were performed separately for daytime and nighttime symptoms for the following periods relative to the start of treatment: baseline during the run-in-period of 2 weeks before treatment; treatment weeks 1 and 2 (period 1); weeks 3 to 5 (period 2), and week 6 until the end of treatment (period 3). The mean total daily symptom score was calculated for each of the above periods, and after having checked the normality assumptions for parametric analyses, comparisons between treatments were made with analysis of covariance, allowing for effects due to baseline mean total daily symptom score, treatment, age, and sex.

For individual nasal symptoms, the median value for each symptom and subject was calculated, and these median values were compared between treatment groups by using the Van Elteren extension to the Wilcoxon rank sum test, stratifying for baseline.

The secondary study endpoint, EG2⁺ eosinophilic inflammation, was evaluated separately for epithelium and subepithelium. The Wilcoxon signed-rank test was used to analyze pollen-induced changes in EG2⁺ eosinophil numbers from pre-season to in-season samples, and comparisons between treatment groups were made by using analysis of covariance.

A *P* value less than .05 was considered to indicate a significant difference.

RESULTS

The grass pollen season in the study area, together with the study design, is shown in Fig 1. The total amount of grass pollen counts during the study period was approximately 17% to 33% higher compared with those of recent grass pollen seasons in the area (personal communication, Maret Saar, Tartu Aerobiology Station).

The patients in the different treatment groups resembled each other regarding age, sex distribution, and duration of allergic rhinitis (Table I).

Symptoms

No statistically significant differences between treatment groups were observed during the run-in period. Compared with the mean symptom scores of the run-in period, the grass pollen season induced a significant increase in the mean overall nasal symptom scores starting from the 11th day of treatment (Fig 2). The effect of different treatments on symptom scores was evaluated separately for daytime and nighttime symptoms for treatment weeks 1 to 2 (period 1), weeks 3 to 5 (period 2), and week 6 until the end of treatment (period 3).

For daytime symptoms, both FPANS and the combination of montelukast and loratadine significantly attenuated the development of nasal symptoms compared with that seen in placebo-treated patients during all 3 evaluation periods (mean $\pm$ SEM differences; period 1: FPANS vs placebo -2.1 ± 0.7 [*P* = .003], montelukast-loratadine vs placebo -1.4 ± 0.6 [*P* = .04]; period 2: -3.2 ± 0.9 [*P* = .001] and -1.9 ± 0.9 [*P* = .04], respectively; period 3: -2.2 ± 0.5 [*P* < .001] and -1.8 ± 0.5 [*P* < .001], respectively). During period 3, FPANS-treated patients had significantly lower symptom scores compared with patients treated with montelukast only (-1.1 ± 0.5 , *P* = .046), whereas montelukast provided significantly better symptom protection compared with that provided by placebo (-1.1 ± 0.5 , *P* = .03). No statistically significant differences in daytime symptoms were observed between patients treated with FPANS or with combined montelukast-loratadine treatment, although there was a consistent trend toward lower total symptom scores in FPANS-treated patients (Table II and Fig 2).

For nighttime symptoms, FPANS-treated patients had significantly lower symptom scores compared with patients receiving placebo treatment for all evaluation periods (-1.4 ± 0.6 [*P* = .02], -2.6 ± 0.8 [*P* = .002], and -1.9 ± 0.5 [*P* < .001], respectively), compared with the

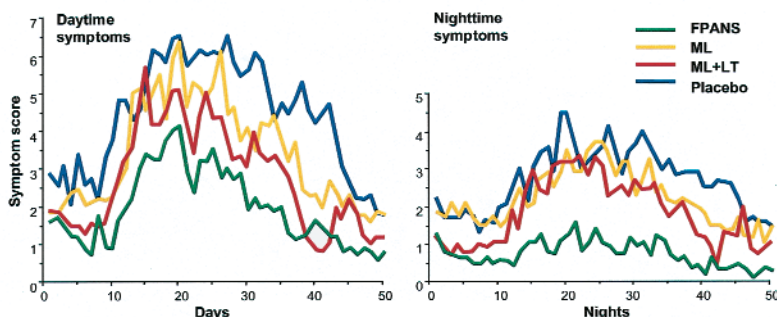


FIG 2. Mean daytime (left panel) and nighttime (right panel) symptom scores in patients with grass pollen-induced allergic rhinitis treated for 50 days with FPANS (200 μ g/d), montelukast (ML; 10 mg/d), a combination of montelukast and loratadine (ML+LT; 10 mg/d), or placebo.

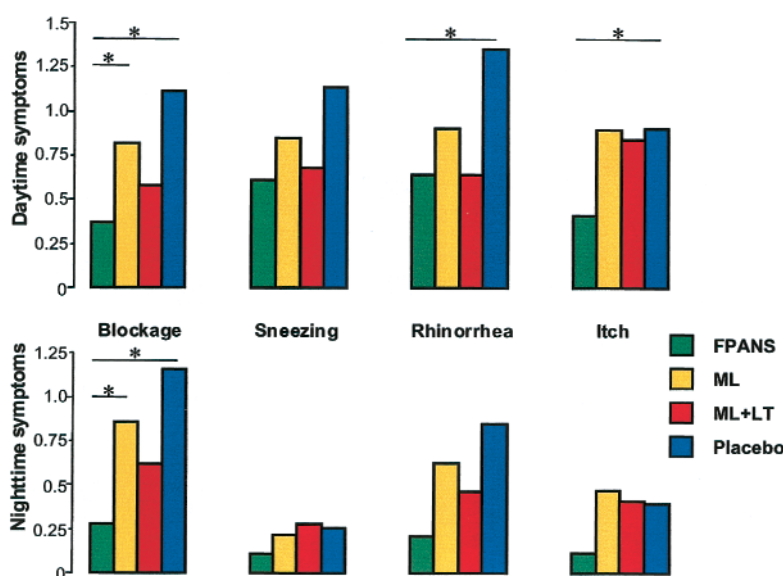


FIG 3. Mean symptom score for nasal blockage, sneezing, rhinorrhea, and nasal itching in patients with allergic rhinitis treated with FPANS, montelukast (ML), a combination of montelukast and loratadine (ML+LT), or placebo (* $P < .05$).

combination of montelukast and loratadine during the peak season at period 2 (-1.7 ± 0.8 , $P = .04$), and compared with montelukast only at periods 2 and 3 (-1.9 ± 0.8 [$P = .02$] and -1.2 ± 0.5 [$P = .01$]). The combination of montelukast and loratadine provided significantly better symptom protection compared with that provided by placebo only at period 3 (-1.1 ± 0.4 , $P = .02$), whereas no significant differences in nighttime symptoms were detected between montelukast and placebo treatments (Table II and Fig 2).

The statistical analysis of individual symptoms of nasal blockage, itching, rhinorrhea, and sneezing indicated statistically significant differences in daytime and nighttime nasal blockage for FPANS versus montelukast ($P = .025$ and $.04$, respectively) and versus placebo ($P = .002$ and $.005$, respectively), as well as in daytime rhinorrhea and itching for FPANS versus placebo ($P = .01$

and $.04$, respectively), in favor of FPANS in all cases (Fig 3). No significant differences between groups were observed in the use of rescue medication.

Local eosinophilic inflammation

Numbers of EG2⁺ eosinophils were evaluated separately for the epithelium and within 200 μ m of the subepithelium. There were no statistically significant differences among the 4 treatment groups in EG2⁺ eosinophil counts in preseason nasal biopsy samples. The grass pollen season induced a significant increase in the numbers of EG2⁺ eosinophils both in the epithelium and subepithelium in patients treated either with placebo, montelukast, or montelukast-loratadine ($P < .01$ in all cases, Wilcoxon signed-rank test). No such increase was observed in patients treated with nasal FPANS ($P = .2$ for epithelium and $P = .5$ for subepithelium). The median

TABLE II. Total daytime and nighttime symptom scores in patients with allergic rhinitis treated with FPANS, montelukast, a combination of montelukast and loratadine, or placebo over the grass pollen season

	Baseline	Weeks 1-2	Weeks 3-5	Weeks 6-8
Daytime scores				
FPANS	1.5 ± 1.4	1.4 ± 0.7*	2.6 ± 1.0*	1.1 ± 0.5*‡
Montelukast	1.9 ± 2.1	2.6 ± 0.5	4.4 ± 0.6	2.2 ± 0.4*
Montelukast-loratadine	1.9 ± 1.5	2.1 ± 0.5*	4.0 ± 0.7*	1.5 ± 0.4*
Placebo	2.4 ± 2.3	3.5 ± 0.4	5.9 ± 0.6	3.3 ± 0.3
Nighttime scores				
FPANS	0.9 ± 1.2	0.7 ± 0.6*	1.0 ± 0.8*‡	0.4 ± 0.5*‡
Montelukast	1.8 ± 1.8	1.8 ± 0.4	2.8 ± 0.5	1.5 ± 0.3
Montelukast-loratadine	1.3 ± 1.2	1.3 ± 0.4	2.7 ± 0.6	1.2 ± 0.3*
Placebo	1.5 ± 1.5	2.1 ± 0.4	3.6 ± 0.5	2.3 ± 0.3

Data are shown as means ± SD for baseline and as adjusted means ± SEM in the remaining cases. Symbols indicate significantly lower mean symptom scores compared with placebo-treated (*), combined montelukast and loratadine-treated (‡), or only montelukast-treated (‡) patients.

pollen-induced increase in the numbers of EG2⁺ eosinophils was 0 cells/mm² in FPANS-treated patients, 22.5 cells/mm² in montelukast-treated patients, 36.2 cells/mm² in montelukast-loratadine-treated patients, and 24.4 cells/mm² in placebo-treated patients for epithelial cell counts and 1.2, 45.7, 46.8, and 76.0 cells/mm², respectively, for subepithelial cell counts. The median pollen-induced increase in epithelial cell counts in FPANS-treated patients was significantly lower compared with that in montelukast-treated patients ($P = .004$, Wilcoxon rank sum test), montelukast-loratadine-treated patients ($P = .02$), and placebo-treated patients ($P < .001$). However, for subepithelial cell counts, the median pollen-induced increase was not significantly different among these treatment groups (Fig 4).

DISCUSSION

In an attempt to provide new treatment options for patients with allergic rhinitis, a combination of 2 mediator-targeted drugs, antihistamines and antileukotrienes, has been suggested as a theoretically promising therapeutic approach. However, the present study demonstrates that, compared with such a combination therapy, the intranasally administered glucocorticoid FPANS provides significantly better protection against development of local eosinophilic inflammation and also significantly better symptom prevention, particularly during the peak of the pollen season.

After demonstration that combined montelukast and loratadine provided statistically significantly better symptom protection compared with that of each of these antimedator treatments alone,¹² the clinical significance of that additive effect remained to be evaluated. In the present study we used one approach for that evaluation, comparing the effect of combined antihistamine-antileukotriene directly to the most efficacious and safe

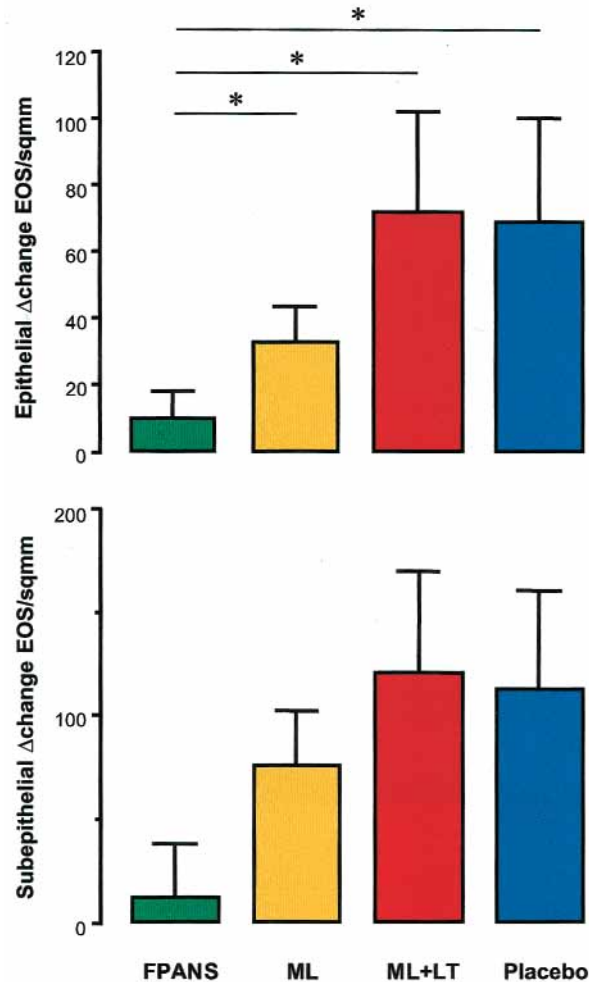


FIG 4. The grass pollen-induced change (means ± SEMs) in the number of EG2⁺ epithelial and subepithelial eosinophils per square millimeter (EOS/sqmm) in nasal biopsy specimens of patients with allergic rhinitis treated with FPANS, montelukast (ML), a combination of montelukast and loratadine (ML+LT), or placebo (* $P < .05$).

allergic rhinitis treatment available, which is nasally administered glucocorticoids. Although for daytime symptoms there was only a trend toward a better effect of intranasal glucocorticoid, it provided significantly better symptom protection for nighttime symptoms. These findings should be interpreted also in the view of the unusually severe pollen season for the study area, with total grass pollen counts being 17% to 33% higher than in a couple of previous seasons. Consequently, in the 2 studies with the similar symptom-recording scale performed during the previous grass pollen seasons, the placebo-treated patients reported only 46% to 65% of daytime peak season symptoms compared with the placebo-treated patients in the present study, whereas nighttime symptoms corresponded more to the results of those regular seasons (data on file).⁴

A somewhat surprising finding in our study was that patients receiving treatment with nasal glucocorticoid experienced significantly less nasal blockage compared

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with that seen in patients treated with the antileukotriene. Previously performed studies on intranasal administration of leukotrienes have implicated the primary role of this mediator in the induction of nasal blockage,⁹⁻¹¹ with limited effect on other rhinitis symptoms. Furthermore, in a clinical situation, when patients with allergic rhinitis were exposed to ragweed pollen for 2 days in a park at the peak of ragweed season, the most consistent benefit provided by a leukotriene receptor antagonist was improvement of nasal congestion.³ Similarly, blocking the leukotriene pathway by using a 5-lipoxygenase inhibitor attenuated nasal congestion but not sneezing.¹⁵ On the basis of that knowledge, we were particularly interested in the effect of treatment on nasal blockage, and therefore the scale used for recording blockage symptoms was more specified compared with that for other symptoms. However, here we demonstrate that also for nasal blockage, patients can expect to get better relief with intranasal glucocorticoids than with antileukotriene treatment. Such an effective reduction of nasal blockage symptoms by local glucocorticoids is well in line with previous reports.^{16,17}

As with symptoms, treatment with a nasal glucocorticoid also provided significantly better protection against the pollen-induced development of nasal eosinophilia compared with that of other treatment groups. This was most evident for the epithelial eosinophil counts, with in-season eosinophils being present in only 2 of 13 FPANS-treated patients. Such an almost total abolishment of pollen-induced epithelial eosinophilia after treatment with nasal glucocorticoids is consistent with earlier reports.¹⁸ Although leukotrienes have been suggested to be involved in the recruitment of eosinophils to the site of inflammation,¹⁹ and some anti-inflammatory effects of antileukotrienes have also been demonstrated in clinical settings,^{20,21} their effect on eosinophilic infiltration has been weak and statistically nonsignificant in several studies.^{4,22} This discrepancy can likely be explained by a recent study in patients with allergic asthma, demonstrating that 5-lipoxygenase inhibition reduced allergen challenge-induced increase in bronchoalveolar lavage eosinophil counts in patients producing high leukotriene levels in bronchoalveolar lavage fluid but not in low leukotriene producers.²³ It is not known whether such a phenomenon applies also to patients with allergic rhinitis and whether a subpopulation of patients with rhinitis can thereby have reduced local eosinophilic inflammation after treatment with antileukotrienes. In line with lack of anti-inflammatory effect of antihistamines, the combination treatment of an antileukotriene plus an antihistamine did not provide any better protection against the development of local eosinophilia compared with treatment with antileukotriene alone. Thus with our current knowledge, local glucocorticoids remain the most effective treatment to reduce mucosal eosinophilic inflammation in patients with allergic rhinitis, achieving their anti-inflammatory effect through a variety of mechanisms.²⁴⁻²⁶

In conclusion, this study shows that FPANS is more effective than the combination of montelukast and lorata-

dine in reducing pollen-induced rhinitis symptoms and nasal mucosal eosinophilic inflammation. Thus local treatment with glucocorticoids, rather than the combination of an antihistamine and an antileukotriene, should be a cornerstone treatment in seasonal allergic rhinitis.

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REFERENCES

- Meltzer EO. The prevalence and medical and economic impact of allergic rhinitis in the United States. *J Allergy Clin Immunol* 1997;99:S805-28.
- 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:S147-334.
- Donnelly AL, Glass M, Minkwitz MC, Casale TB. The leukotriene D₄-receptor antagonist, ICI 204,219, relieves symptoms of acute seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1995;151:1734-9.
- Pullerits T, Praks L, Skoogh BE, Ani R, Lötvalld J. Randomized placebo-controlled study comparing a leukotriene receptor antagonist and a nasal glucocorticoid in seasonal allergic rhinitis. *Am J Respir Crit Care Med* 1999;159:1814-8.
- Weiner JM, Abramson MJ, Puy RM. Intranasal corticosteroids versus oral H₁ receptor antagonists in allergic rhinitis: systematic review of randomized controlled trials. *BMJ* 1998;317:1624-9.
- Stempel DA, Thomas M. Treatment of allergic rhinitis: an evidence-based evaluation of nasal corticosteroids versus nonsedating antihistamines. *Am J Managed Care* 1998;4:89-96.
- Foresi A. A comparison of the clinical efficacy and safety of intranasal fluticasone propionate and antihistamines in the treatment of rhinitis. *Allergy* 2000;55(suppl 62):12-4.
- Howarth PH. Mediators of nasal blockage in allergic rhinitis. *Allergy* 1997;52(suppl 40):12-8.
- 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;16:289-97.
- Miadonna A, Tedeschi A, Leggieri E, Lorini M, Folco G, Sala A, et al. Behavior and clinical relevance of histamine and leukotrienes C₄ and B₄ in grass pollen-induced rhinitis. *Am Rev Respir Dis* 1987;136:357-62.
- Okuda M, Watase T, Mezawa A, Liu CM. The role of leukotriene D₄ in allergic rhinitis. *Ann Allergy* 1988;60:537-40.
- Meltzer EO, Malmstrom K, Lu S, Prenner BM, Wei LX, Weinstein SF, et al. Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: a randomized, placebo-controlled clinical trial. *J Allergy Clin Immunol* 2000;105:917-22.
- Lis K, Malmstrom K, Nayak AS, Philip G, Malice MP, Reiss TF, et al. Treatment of fall allergic rhinitis with montelukast alone or in combination with loratadine in a multicenter, double-blind, randomized, placebo-controlled study [abstract]. *J Allergy Clin Immunol* 2001;107:S158.
- Reicin A, White R, Weinstein SF, Finn AF Jr, Nguyen H, Peszek I, et al. Montelukast, a leukotriene receptor antagonist, in combination with loratadine, a histamine receptor antagonist, in the treatment of chronic asthma. *Arch Intern Med* 2000;160:2481-8.
- Knapp HR. Reduced allergen-induced nasal congestion and leukotriene synthesis with an orally active 5-lipoxygenase inhibitor. *N Engl J Med* 1990;323:1745-8.
- Darnell R, Pecoud A, Richards DH. A double-blind comparison of fluticasone propionate aqueous nasal spray, terfenadine tablets and placebo in the treatment of patients with seasonal allergic rhinitis to grass pollen. *Clin Exp Allergy* 1994;24:1144-50.
- Jordana G, Dolovich J, Briscoe MP, Day JH, Drouin MA, Gold M, et al. Intranasal fluticasone propionate versus loratadine in the treatment of adolescent patients with seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;97:588-95.
- Jacobson MR, Juliusson S, Löwhagen O, Balder B, Kay AB, Durham SR. Effect of topical corticosteroids on seasonal increases in epithelial eosinophils and mast cells in allergic rhinitis: a comparison of nasal brush and biopsy methods. *Clin Exp Allergy* 1999;29:1347-55.

19. Laitinen LA, Laitinen A, Haahtela T, Vilkkä V, Spur BW, Lee TH. Leukotriene E4 and granulocytic infiltration into asthmatic airways. *Lancet* 1993;341:989-90.
20. Wenzel SE, Trudeau JB, Kaminsky DA, Cohn J, Martin RJ, Westcott JY. Effect of 5-lipoxygenase inhibition on bronchoconstriction and airway inflammation in nocturnal asthma. *Am J Respir Crit Care Med* 1995;152:897-905.
21. Kane GC, Pollice M, Kim CJ, Cohn J, Dworski RT, Murray JJ, et al. A controlled trial of the effect of the 5-lipoxygenase inhibitor, zileuton, on lung inflammation produced by segmental antigen challenge in human beings. *J Allergy Clin Immunol* 1996;97:646-54.
22. Calhoun WJ, Lavins BJ, Minkwitz MC, Evans R, Gleich GJ, Cohn J. Effect of zafirlukast (Accolate) on cellular mediators of inflammation: bronchoalveolar lavage fluid findings after segmental antigen challenge. *Am J Respir Crit Care Med* 1998;157:1381-9.
23. Hasday JD, Meltzer SS, Moore WC, Wisniewski P, Hebel JR, Lanni C, et al. Anti-inflammatory effects of zileuton in a subpopulation of allergic asthmatics. *Am J Respir Crit Care Med* 2000;161:1229-36.
24. Schleimer RP, Bochner BS. The effects of glucocorticoids on human eosinophils. *J Allergy Clin Immunol* 1994;94:1202-13.
25. Bradding P, Feather IH, Wilson S, Holgate ST, Howarth PH. Cytokine immunoreactivity in seasonal rhinitis: regulation by a topical corticosteroid. *Am J Respir Crit Care Med* 1995;151:1900-6.
26. Pullerits T, Lindén A, Praks L, Cardell LO, Lötval J. Upregulation of nasal mucosa eotaxin in patients with allergic rhinitis during grass pollen season: effect of a local glucocorticoid. *Clin Exp Allergy* 2000;30:1469-75.