
Effect of montelukast on symptoms and exhaled nitric oxide levels in 7- to 14-year-old children with seasonal allergic rhinitis

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Background: Cysteinyl leukotrienes have been found to exert potent inflammatory effects in the upper airways and play a fundamental role in the pathogenesis of allergic rhinitis. Previous studies have reported increased levels of exhaled nitric oxide (eNO) in patients with allergic rhinitis without asthma symptoms.

Objective: To investigate the role of treatment with montelukast on symptoms, eNO levels, and peripheral eosinophil counts of children with seasonal allergic rhinitis during pollen season.

Methods: A randomized, double-blind, parallel-group study performed between April and June 2005 in 57 children aged 7 to 14 years with seasonal allergic rhinitis was performed. The study comprised a 1-week screening period, a 1-week run-in period, and a 2-week treatment period with once daily montelukast, 5 mg, or matching placebo.

Results: No significant difference at baseline was found in symptom scores, eNO levels, and blood eosinophil counts between the treatment and placebo groups. After 2 weeks of montelukast treatment, improvements from the baseline in the daytime nasal, composite, and daytime eye symptoms scores were significantly greater in the montelukast group compared with the placebo group ($P < .001$, $P < .001$, and $P < .01$, respectively). A significant decrease was also found in eosinophil counts ($P < .001$) in the montelukast group compared with the placebo group after treatment. Montelukast treatment did not produce a significant effect on eNO levels compared with placebo ($P = .96$).

Conclusion: Montelukast treatment provided significant improvement in symptoms and peripheral eosinophil counts of school-age children with seasonal allergic rhinitis; however, it did not show a significant effect on eNO levels.

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INTRODUCTION

Allergic rhinitis is the most common chronic condition in both the adult and pediatric populations, affecting 10% to 30% of adults and 20% to 40% of children.¹ Specific therapies for allergic rhinitis included in the recommendations are antihistamines, oral and nasal decongestants, intranasal corticosteroids, intranasal cromolyn, intranasal anticholinergics, and, in patients with severe symptoms, immunotherapy and oral corticosteroids.² Cysteinyl leukotrienes have been found to exert potent inflammatory effects in the upper airways and play a fundamental role in the pathogenesis of allergic rhinitis.³ With the Food and Drug Administration's approval of montelukast in January 2003 for seasonal allergic rhinitis,⁴ another treatment option to relieve the signs and symptoms of allergic rhinitis became available. Studies in adult patients with seasonal allergic rhinitis indicate that montelukast improves daytime and nighttime symptoms of allergic rhinitis, as well as quality-of-life parameters and peripheral blood eosinophil counts, when administered alone⁵⁻⁸ or concomitantly with antihistaminics.^{9,10}

Exhaled nitric oxide (eNO) has been proposed as a potential indirect marker of inflammation in the lower airways.^{11,12}

The previously reported, increased levels of eNO in patients with allergic rhinitis without asthma symptoms indicate that there is some degree of eosinophilic inflammation in the lower airways in addition to the upper airways.¹³⁻¹⁶ We hypothesize that if there is lower airway inflammation demonstrated as increased eNO levels in seasonal allergic rhinitis, montelukast, as a systemic anti-inflammatory drug, may decrease these elevated eNO levels.

To our knowledge, no studies have examined the effectiveness of montelukast alone on symptoms, eNO levels, and peripheral eosinophil counts in children with seasonal allergic rhinitis. Therefore, the aim of this study was to investigate the role of treatment with montelukast, 5 mg given once daily for 2 weeks, on these parameters.

MATERIALS AND METHODS

Patients

Patients were 7 to 14 years old and had a well-documented clinical history of seasonal allergic rhinitis for at least 2 years with exacerbations during the spring pollen season. Patients had to exhibit a positive skin prick test result (wheal diameter at least 3 mm greater than negative control) to one of the regional allergens active during the study season, as well as daytime nasal symptoms of at least mild-to-moderate severity as rated daily by patients (cumulative score of at least 18 during a 7-day run-in period).

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Patients diagnosed as having bronchial asthma (forced expiratory volume in 1 second <80% of the predicted normal value, an increase in forced expiratory volume in 1 second of at least 12% after bronchodilator inhalation, and asthma symptoms such as wheezing, chronic cough, chest tightness, exercise-induced wheeze, or dyspnea in history) and/or allergic rhinitis who had mite, mold, cat, and cockroach sensitivity on skin prick tests, who experienced rhinitis outside the pollen season, or who used specific immunotherapy were not eligible for inclusion. Additional exclusion criteria included substantial, structural nasal obstruction and upper respiratory tract infection, sinusitis, or ocular infection within 4 weeks before the trial.

Patients who required medication other than the study medication for treatment of allergic rhinitis were removed from the study. Medications that were prohibited for pre-specified times before the study and during the study included systemic, inhaled, nasal, or ophthalmic corticosteroids; short- and long-acting β -adrenergic agonists; nasal, ophthalmic, and inhaled cromolyns; nonsteroidal anti-inflammatory agents; topical or systemic antihistamines and decongestants; theophylline; and inhaled anticholinergics.

Seventeen age-matched, healthy children with no history of asthma, allergic rhinitis, atopic eczema, or other relevant disease, who were not receiving any medications, were recruited as the control group. All of them were atopic, as defined by at least one positive skin test result for common airborne allergens.

Study Design

This randomized, double-blind, parallel-group study was performed between April and June 2005 in the outpatient department of Gazi University in Ankara, Turkey. The study comprised a 1-week screening period (outside the grass pollen season), a 1-week run-in period (during early pollen season), and a 2-week treatment period (during the peak pollen season). After an initial screening visit, patients participated in a 1-week run-in period when daytime nasal symptoms, nighttime symptoms, and daytime eye symptoms were recorded. Patients were reevaluated at the end of this run-in period and were allocated in a randomized, double-blind, placebo-controlled, parallel fashion to a 2-week treatment period with once daily montelukast, 5 mg, or matching placebo. Patients received one tablet each day of the 2-week treatment period. Montelukast and placebo tablets were taken at bedtime irrespective of food. Montelukast and placebo tablets were identical in appearance and prepared in the laboratories of the Faculty of Pharmacy of Gazi University. The allocation schedule was also created and concealed at the same place and broken at the study end. Compliance was evaluated by diary cards and returned tablet counts in the 2-week treatment period. Peripheral blood eosinophil counts and eNO levels were measured before and at the end of the 2-week treatment period. The baseline eNO levels were also compared with those of healthy atopic controls. The study was approved by ethical review committee of Gazi Univer-

sity, Faculty of Medicine, and all patients gave written informed consent before the study started.

Daily Symptom Evaluation

All patients completed a daily diary during the run-in and treatment periods and scored each symptom on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe symptoms).^{5,6} Composite symptoms score were defined as the mean of 2 components: daytime nasal symptoms score (average of nasal congestion, rhinorrhea, sneezing, and itching, each rated on a 0- to 3-point scale) and nighttime symptoms score (average of nasal congestion on awakening, difficulty going to sleep, and nighttime awakenings, each rated on a 0- to 3-point scale). Also measured was the daytime eye symptoms score (average of the individual symptoms of tearing, itching, red, and puffy eyes).

Pollen Count

Pollen grains were collected in the study area during the season by means of a 7-day recording volumetric trap (Burkard, Rickmansworth, England). Pollen counts were expressed as the total weekly count of particles per cubic meter of air (Figure 1).

Blood Eosinophil Measurements

Peripheral blood eosinophil counts were measured by using a Cell-Dyne 4000 hematological autoanalyzer (Abbott Laboratories, Chicago, IL).

eNO Measurement

We measured eNO levels after a run-in period during natural pollen exposure in our patients when their allergic rhinitis symptoms began. The eNO was measured with a fast response chemiluminescence analyzer (NOA Tm 280i, Sievers Instruments Inc, Boulder, CO) by the on-line single-breath technique, according to the European Respiratory Society/American Thoracic Society (ERS/ATS) recommendations for children.¹⁷ The analyzer has an NO sampling rate of 200 mL/min, a detection range of less than 0.1 to 500,000 ppb, and a response time of 0.02 second for 90% full scale. Briefly, the patients were asked to perform a single slow

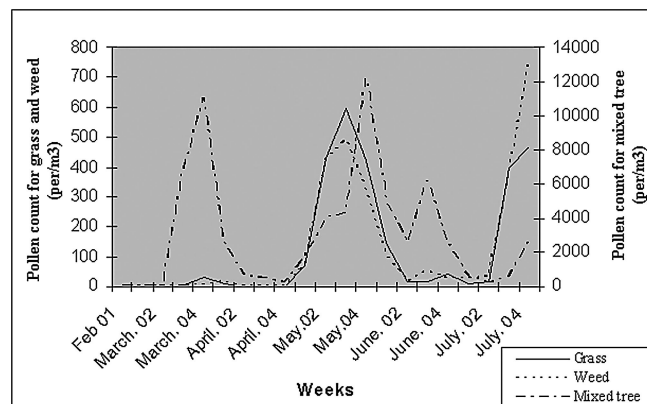


Figure 1. Weekly grass pollen counts for spring in the study area.

exhalation starting from total lung capacity through a mouth-piece and a 1-way nonrebreathing valve against a resistance of 16 cm H₂O under a visual biofeedback to maintain a 50-mL/s steady flow. Patients were at rest and sitting down, had refrained from eating and exercise for at least 1 hour, and had breathed NO-free air (99.5% oxygen containing <1 ppb of NO) without a nose-clip before the single exhalation maneuver. Ambient air NO was recorded before and after each test. The analyzer was calibrated daily with a zero signal (air filter scrubber, potassium permanganate, and charcoal; ACT 01400, Sievers Instruments Inc) and certified NO gas containing 10 ppm of NO gas (BOS Mitan, Ankara, Turkey). The eNO levels were measured at the plateau (≥ 2 seconds during an exhalation of ≥ 6 seconds) of the end exhaled reading and expressed as parts per billion. At least 3 measurements that varied by less than 10% or 2 measurements that varied by less than 5% were recorded. The mean value of the respective plateau was retained according to specific guidelines.¹⁷

Safety

Safety and tolerability were evaluated by adverse event reporting and by changes in vital signs and physical examination between the first visit and the final visit.

Statistical Analysis

All analysis were performed using SPSS statistical software, version 11.5 (SPSS Inc, Chicago, IL). The χ^2 test was used for categorical variables and expressed as observation count. Because the variables were not distributed normally, non-parametric statistics were used throughout the study. Data were expressed as median and 25th to 75th percentiles. Within-group comparisons were made with the Wilcoxon test; between-group differences were analyzed with the Mann-Whitney *U* test. The Spearman rank test was used to deter-

mine correlations. All *P* values were 2-tailed, and *P* < .05 was considered statistically significant.

Power and Sample Size

The study was designed to detect a pairwise between-treatment difference of 0.25 in score change from baseline in the mean daytime nasal symptoms score (α error of .05; 2-sided test; and a β error of .10; ie, with power of 90%) with a sample size of 21 patients per group. The between-treatment difference of 0.25 was estimated from other allergic rhinitis trials using similar 4-point scales (0 to 3 points).^{9,18}

RESULTS

Patients

At baseline 81 patients were screened, 66 were included in the study, and 57 (29 in the montelukast group and 28 in the placebo group) completed the study. A total of 9 patients discontinued treatment after allocation (protocol deviation, 1 and 1; loss to follow-up, 2 and 3; and patient withdrew consent, 1 and 1 in the montelukast and placebo groups, respectively). The rates and reasons for discontinuation were similar among the treatment groups. At the end of treatment, rates of medication compliance in the 2 groups as measured by tablet counts and diary cards were similar (96.6% in the montelukast group and 95.5% in the placebo group). Baseline patient characteristics, including demographics, allergy history, and baseline efficacy scores, are listed in Table 1. The median age of the patients was 11.50 years (range, 10.00–12.75 years), and most were boys (56.1%). The median duration of allergic rhinitis was 3.0 years (range, 3.0–5.0 years), and the median cumulative score of daytime nasal symptoms was 45.00 (range, 40.12–56.00) during the 7-day run-in period. No clinically and statistically meaningful differences were found in any baseline characteristics between

Table 1. Characteristics and Baseline Values of Patients in Each Treatment Group

Variable	Control group	Placebo group (n = 28)	Montelukast group (n = 29)	<i>P</i> value*
Age, mean (range), y	11.50 (8.00–13.00)	11.42 (10.29–12.67)	11.50 (9.88–13.04)	.76
Sex, No. (%)				
Male	8 (47)	14 (50)	18 (62)	.36
Female	9 (53)	14 (50)	11 (38)	
Duration of allergic rhinitis, mean (range), y		3 (3–5)	3 (3–5)	.67
Daytime nasal symptoms score†‡		1.50 (1.19–1.93)	1.75 (1.32–1.94)	.32
Nighttime symptoms score†‡		0.00 (0.00–0.17)	0.00 (0.00–0.11)	.54
Composite symptoms score†‡		0.78 (0.62–1.10)	0.87 (0.66–1.06)	.56
Daytime eye symptoms score†‡		0.75 (0.25–1.48)	1.03 (0.60–2.12)	.23
eNO, ppb‡	12.30 (8.75–21.20)	28.00 (19.92–51.17)§	29.60 (23.00–42.65)§	.80
Peripheral blood eosinophil count, $\times 10^3$ cells/mL‡		226.5 (146.0–459.0)	246.0 (161.0–445.0)	.77

Abbreviation: eNO, exhaled nitric oxide.

* *P* value is for the comparison of montelukast vs placebo.

† Mean score during the run-in period; all symptoms were scored on a 0- (none) to 3-point (severe) scale.

‡ Values are shown as median (25th–75th percentiles).

§ *P* value for control group vs montelukast is <.001 and for control group vs placebo is <.001.

the treatment groups and the control group except eNO levels (Table 1).

Efficacy

Improvements over baseline in the daytime nasal symptoms score ($P < .001$), all individual domains of the daytime nasal symptoms score (nasal congestion, $P < .001$; rhinorrhea, $P < .001$; sneezing, $P < .001$; and itching, $P < .001$), composite symptoms score ($P < .001$), daytime eye symptoms score ($P < .001$), and 3 of 4 individual domains of the daytime eye symptoms score (tearing, $P = .006$; itching, $P < .001$; and redness, $P = .01$) were statistically significant in the montelukast group. Improvements over baseline in the daytime nasal symptoms score, all individual domains of the daytime nasal symptoms score, composite symptoms score, daytime eye symptoms score, and all individual domains of the daytime eye symptoms score were not statistically significant in the placebo group ($P > .05$).

Improvements from the baseline in the daytime nasal symptoms score, composite symptoms score, and daytime eye symptoms score were significantly greater in the montelukast group compared with the placebo group ($P < .001$, $P < .001$, and $P < .01$, respectively). Montelukast showed significantly greater effect than placebo on all of the individual domains of the daytime nasal symptoms score (nasal congestion, rhinorrhea, sneezing, and itching) and 2 individual domains of the daytime eye symptoms score (tearing and pruritus). Changes in median scores from baseline to the end of the second week of the treatment period and differences from placebo for the daytime nasal symptoms score, composite symptoms score, daytime eye symptoms score, and individual domains of daytime nasal symptoms and daytime eye symptoms are provided in Table 2 and Figure 2.

Nine patients in the montelukast group (31%) and 12 patients in the placebo group (43%) had nighttime symptoms, all of which were graded as mild in severity. Nighttime

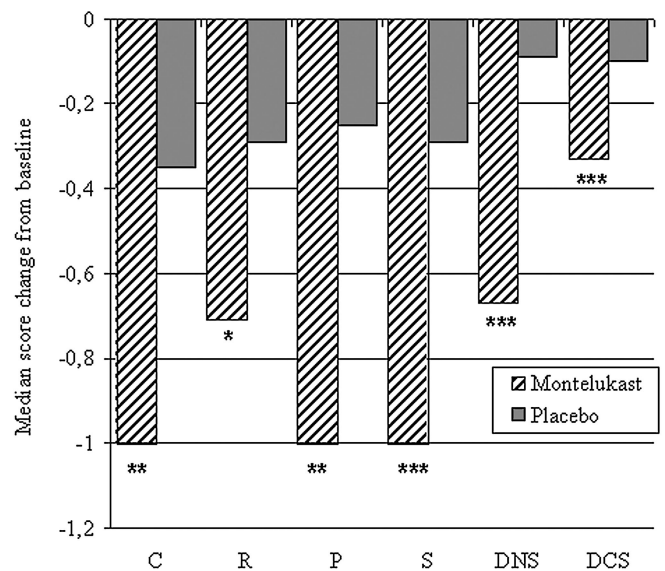


Figure 2. Median score change from baseline until more than 2 weeks of treatment. C indicates congestion; R, rhinorrhea; P, pruritus; S, sneezing; DNS, daytime nasal symptoms; and DCS, daily composite symptoms. Symptoms are rated on a scale of 0 (none) to 3 (severe). * $P = .01$, ** $P = .001$, *** $P < .001$ compared with placebo.

symptoms scores were not found to be significantly different 2 weeks after treatment compared with baseline within each treatment groups ($P = .15$ for the montelukast group and $P = .07$ for the placebo group). Compared with placebo, 2 weeks of treatment with montelukast had no significant effect on nighttime symptoms scores ($P = .79$).

At baseline, the median eNO levels were found to be significantly higher in children with allergic rhinitis compared with healthy atopic controls (median, 28.20 ppb; 25th-

Table 2. Changes of Study Parameters From Baseline After the 2-Week Treatment Period*

Parameter	Montelukast group	Placebo group	P value
Daytime nasal symptoms†	-0.67 (-0.93 to -0.34)	-0.03 (-0.27 to -0.22)	<.001
Congestion	-1.00 (-1.00 to -0.42)	-0.29 (-0.67 to 0.00)	.001
Rhinorrhea	-0.58 (-1.00 to -0.16)	-0.22 (-0.54 to -0.10)	.010
Pruritus	-1.00 (-1.00 to -0.42)	-0.25 (-0.68 to 0.00)	.001
Sneezing	-1.00 (-1.14 to -0.50)	-0.29 (-0.43 to 0.00)	<.001
Daily composite symptoms‡	-0.32 (-0.64 to -0.14)	-0.04 (-0.13 to -0.11)	<.001
Daytime eye symptoms	-0.50 (-0.82 to -0.01)	-0.07 (-0.25 to -0.21)	.01
Tearing	-0.14 (-1.14 to 0.00)	0.00 (-0.21 to -0.39)	.005
Pruritus	-0.42 (-1.57 to 0.00)	0.00 (-0.42 to -0.39)	.005
Redness	-0.57 (-1.00 to 0.00)	-0.07 (-0.42 to 0.00)	.16
Puffiness	0.00 (0.00 to 0.00)	0.00 (0.00 to 0.00)	.81
Eosinophil count, % decrease	-52.23 (-74.48 to -1.77)	-7.07 (-6.91 to 28.78)	<.001
eNO	-0.03 (-0.36 to 0.27)	-0.10 (-0.26 to 0.46)	.96

Abbreviation: eNO, exhaled nitric oxide.

* Data are presented as median (25th-75th percentiles).

† Mean score during 2-week blinded treatment period; all symptoms were scored on a 0- (none) to 3-point (severe) scale.

‡ Mean of the daytime nasal symptoms score and the nighttime symptoms score. P value is for the comparison with placebo.

75th percentiles, 20.60–47.25 ppb; vs median, 12.30; 25th–75th percentiles, 8.75–21.20 ppb; $P < .001$). No significant differences were found in eNO levels within the treatment groups compared with baseline after the 2 weeks of treatment (median eNO levels before and after the treatment: 29.60 ppb; 25th–75th percentiles, 23.00–42.65 ppb; vs 24.80 ppb; 25th–75th percentiles, 19.35–48.25 ppb; $P = .73$; in the montelukast group; and 28.00 ppb; 25th–75th percentiles, 19.92–51.17 ppb; vs 32.95; 25th–75th percentiles, 16.70–66.60 ppb; $P = .70$; in the placebo group). When compared with placebo, 2 weeks of treatment with montelukast had no significant effect on eNO levels ($P = .96$) (Fig 3). The median (25th to 75th percentiles) values of eNO before and after 2 weeks of treatment of montelukast and placebo are summarized in Table 2 and Figure 3.

Peripheral blood eosinophil counts were similar in each group at baseline ($P = .77$ and $P = .97$, respectively). Percentage decreases in eosinophil count after 2 weeks of treatment were -52.23% (25th–75th percentiles, -74.48% to -1.77%) in the montelukast group and -7.07% (25th–75th percentiles, -6.91% to 28.78%) in the placebo group. After 2 weeks of treatment, a decrease in eosinophil counts ($P < .001$) was significant in the montelukast group compared with the placebo group (Table 2).

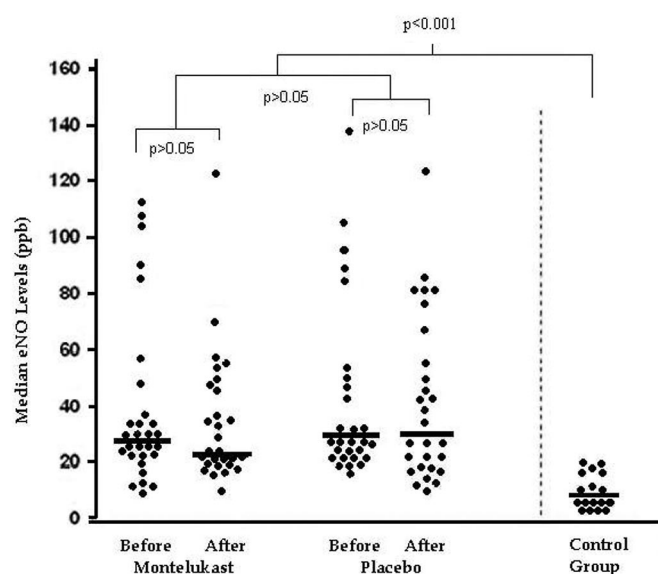


Figure 3. Median exhaled nitric oxide (eNO) levels in each treatment groups. Compared with placebo, no significant difference was found between treatment groups before and after 2 weeks of treatment ($P > .05$). At baseline, median eNO levels were significantly higher in children with allergic rhinitis compared with healthy atopic controls (median, 28.20 ppb; 25th–75th percentiles, 20.60–47.25 ppb; vs median, 12.30; 25th–75th percentiles, 8.75–21.20 ppb; $P < .001$). Median eNO levels before and after the treatment were 29.60 ppb (25th–75th percentiles, 23.00–42.65 ppb) vs 24.80 ppb (25th–75th percentiles, 19.35–48.25 ppb; $P = .73$) in the montelukast group and 28.00 ppb (25th–75th percentiles, 19.92–51.17 ppb) vs 32.95 ppb (25th–75th percentiles, 16.70–66.60 ppb; $P = .70$) in the placebo group.

We did not find any correlation between baseline eNO levels and baseline daytime nasal symptoms score ($r = 0.60$, $P = .65$), nighttime symptoms score ($r = 0.15$, $P = .24$), composite symptoms score ($r = 0.12$, $P = .35$), peripheral eosinophil counts ($r = 0.25$, $P = .06$), and the number ($r = -0.007$, $P = .96$) or diameter ($r = 0.23$, $P = .10$) of positive skin prick test results.

Safety

Clinical adverse experiences occurred only in 3 patients (5%) in the whole group, 2 (7%) in the montelukast group and 1 (4%) in the placebo group. The only reported adverse experience was headache in both treatment groups. No significant difference was found in the incidence of clinical adverse experiences between the treatment groups ($P = .97$). There were no discontinuations because of adverse experiences in either treatment group.

DISCUSSION

This is the first study, to our knowledge, to investigate the effect of montelukast on symptoms of allergic rhinitis and eNO levels in school-age children with seasonal allergic rhinitis without asthma. We found that 5 mg of montelukast administered once daily for 2 weeks during the spring allergy season in 7- to 14-year-old children with seasonal allergic rhinitis produced a significant improvement compared with placebo in daytime nasal symptoms score, daily composite symptoms score, and daytime eye symptoms score but not in nighttime symptoms score. Two-week montelukast therapy failed to suppress eNO levels but reduced peripheral blood eosinophil counts during active pollen season in children with seasonal allergic rhinitis.

The beneficial effect of montelukast on the symptoms of seasonal allergic rhinitis were previously demonstrated in many reports with adult patients. Our results are in line with those of adult studies that consider the daytime nasal and eye symptoms scores.^{3,5–8} One study in children with pollen-induced allergic rhinitis with asthma reported protection against nasal challenge–induced congestion with montelukast but failed to show the same effect in symptoms of patients in the clinical trial.¹⁸ These investigators proposed that this was possibly due to the low pollen counts and mildness of the symptoms. In contrast to the published studies, we could not demonstrate a beneficial effect of montelukast treatment on nighttime symptoms. This finding may be a result of the small number of patients who had nighttime symptoms (9 and 12 patients in the montelukast and placebo groups, respectively).

The significant decrease in peripheral eosinophil counts in the montelukast group, compared with the placebo group, is another important finding of our study. Nasal mucosal exposure to antigen causes local inflammation characterized by infiltration of eosinophils, neutrophils, and mononuclear cells,^{19,20} as well as systemic signs of inflammation such as eosinophilia.²¹ Peripheral blood eosinophilia accompanies natural pollen exposure and the resultant symptoms of aller-

gic rhinitis.^{22,23} The beneficial effect of treatment with montelukast in peripheral blood eosinophils was demonstrated in many studies, including studies of allergic rhinitis^{3,6,8} and asthma.^{24,25} Our results are in line with the result of these studies, suggesting that montelukast has a beneficial effect on systemic allergic inflammation. However, Fabbri et al²⁶ showed that blood eosinophils do not necessarily reflect inflammatory processes in the lung. This may explain why we did not find any correlation between eNO levels and blood eosinophil counts.

It has been previously reported that there might be some degree of lower airway inflammation in seasonal allergic rhinitis without asthma.^{13,16,27} The eNO levels in patients with allergic rhinitis were found to be higher than atopic and nonatopic controls in both adults¹⁵ and children.²⁸ In addition, studies in adult patients demonstrated that eNO levels were increased in patients with allergic rhinitis compared with healthy controls when measurements were performed in^{13,29} and out^{13,30} of pollen season. These findings suggest that eNO may be used as a marker of inflammation in allergic rhinitis, as it is for asthma.³¹ The baseline eNO levels measured in our study were higher than atopic controls somewhat close to asthmatic range. However, previous studies that used the same method of eNO measurement as ours also reported high eNO levels in patients with allergic rhinitis.^{16,32–35} Furthermore, other studies have found no difference in eNO levels between patients with seasonal asthma and patients with seasonal allergic rhinitis.^{13,15} We measured eNO levels after the run-in period during natural pollen exposure in our patients when their allergic rhinitis symptoms began. It is well known that natural allergen exposure during a pollen season results in increased concentration of eNO levels not only in atopic asthmatic patients but also in allergic rhinitis patients without asthma.^{13,27,30,33} We do not think that high eNO levels are due to measurement errors, since we measured eNO levels according to the ATS/ERS recommendations for children.¹⁷ Sinusitis and chronic lower respiratory tract infections known to influence eNO levels had also been excluded in our patients. To our knowledge, no study has yet been performed investigating the effect of montelukast on eNO levels in adults or children with seasonal allergic rhinitis without asthma symptoms. Two studies on the effect of montelukast on eNO levels in adult patients with allergic rhinitis concomitant with asthma reported conflicting results.^{36,37} Both of them compared montelukast with inhaled and intranasal budesonide, and the trials were 2 weeks long. One of the studies³⁶ that used cetirizine in addition to montelukast did not suppress eNO levels, but in the other study³⁷ montelukast was found to be as equally effective as intranasal plus inhaled budesonide on eNO levels. In our study, 2 weeks of montelukast treatment did not decrease eNO levels. However, there are major differences between our study and the 2 studies mentioned herein with respect to study participants and their regular treatment. First, in these 2 studies the study participants were all adults with allergic rhinitis concomitant with asthma. Second, some of the patients included in these studies

were undergoing regular treatment with inhaled steroids. In contrast, our study included only children with allergic rhinitis without asthma, and all of them were steroid naive. We believe that regular treatment with inhaled steroids and concomitant asthma in the previous 2 studies might have affected the results on eNO levels.

Several reasons may explain why we did not find any significant reduction in eNO levels by montelukast treatment. It could be because of the effect of atopy on eNO production in patients with asthma or allergic rhinitis. This is not an entirely new finding; in fact, Gratzou et al¹⁵ detected increased eNO levels only in atopic patients with asthma and/or rhinitis but not in nonatopic patients. Meanwhile, there is also convincing evidence that natural pollen exposure results in increased concentration of eNO in patients with seasonal allergic rhinitis.^{30,38} Prieto et al³⁴ suggested that inhalation of pollens in patients with seasonal allergic rhinitis may have a direct effect on NO production, regardless of the presence of lower airway inflammation, and the presence of atopy may be sufficient to increase eNO levels in patients with allergic rhinitis. In our study, although montelukast decreased rhinitis symptoms significantly, none of the patients were symptom free at the end of the study period. During the study period, grass, weed, and mixed tree pollens reached their peak concentration in our region, and this continuous pollen exposure might have prevented the reduction in eNO levels in our patients.

The relationship between eNO and histologic markers of bronchial inflammation has not yet been studied in patients with allergic rhinitis without asthma. Although eNO is generally accepted as a sensitive marker of eosinophilic airway inflammation in asthma, the magnitude of correlation between eNO and direct measures of airway inflammation is relatively small.^{39,40} In fact, some studies reported no associations between eNO and sputum eosinophil numbers.⁴¹ Also, no relationship could be demonstrated between eNO and mucosal eosinophils in bronchial biopsy specimens of asthmatic patients in a few studies.^{42,43} Sandrini et al¹⁶ reported that nasal triamcinolone showed a significant effect on eNO levels only in patients with allergic rhinitis concomitant with asthma but failed to demonstrate a similar effect in patients with allergic rhinitis alone. Perhaps eNO reflects different aspects of the bronchial inflammatory process.^{27,42} Our study was not designed to detect the effect of montelukast on nasal eosinophils or nasal nitric oxide levels, which may be a limitation of our study. Therefore, we cannot comment on the effect of montelukast on nasal inflammation.

In conclusion, the findings of this study support the use of montelukast in treatment of seasonal allergic rhinitis among 7- to 14-year-old children as in adults. A 5-mg tablet of montelukast taken once daily provided significant benefit in children with seasonal allergic rhinitis in daytime nasal symptoms, daily composite symptoms, and daytime eye symptoms and was well tolerated. However, treatment with montelukast did not show a significant effect on the eNO levels in school-

age children with seasonal allergic rhinitis during the active pollen season.

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