

Efficacy of montelukast during the allergy season in patients with chronic asthma and seasonal aeroallergen sensitivity

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Background: Montelukast has proven efficacy in the treatment of chronic asthma and seasonal allergic rhinitis, but it has not been evaluated in the subpopulation of asthmatic patients with seasonal asthma symptoms.

Objective: To determine the effectiveness of montelukast treatment in improving the control of asthma symptoms during the allergy season in patients with active asthma and seasonal aeroallergen sensitivity.

Methods: Adults with a history of chronic asthma who are also symptomatic during the allergy season and with skin test sensitivity to seasonal aeroallergens were enrolled in a randomized, parallel-group, multicenter study with a 1-week, single-blind, placebo run-in period followed by 3 weeks of double-blind treatment during the spring of 2004. After the run-in period, eligible patients were randomly assigned to receive either oral montelukast (10 mg) or placebo. Daytime and nighttime asthma symptom scores, β -agonist use, and morning and evening peak expiratory flow rates were recorded daily using an electronic diary. The primary end point was mean change from baseline to week 3 in the daytime asthma symptom score.

Results: Of 455 randomized patients, 433 completed the study. Compared with placebo, treatment with montelukast resulted in a significant improvement from baseline in the daytime asthma symptom score (-0.54 vs -0.34 ; $P = .002$) and in β -agonist use, nighttime symptoms, and peak expiratory flow rates. Few patients in the montelukast and placebo groups discontinued study participation because of asthma (1.3% and 3.0%, respectively).

Conclusion: In patients with chronic asthma and seasonal aeroallergen sensitivity, montelukast treatment provided significant asthma control during the allergy season compared with placebo.

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INTRODUCTION

There is evidence that in asthmatic patients with seasonal aeroallergen sensitivity, natural allergen exposure often results in increased airway responsiveness, which may lead to increases in asthma symptoms and the likelihood of exacerbations. Cysteinyl leukotrienes seem to play a role in this process. Cysteinyl leukotriene pathway enzymes are up-regulated in key allergic and inflammatory cells from the nasal lavage of patients with active seasonal allergic rhinitis¹ and in the bronchial mucosa after natural allergen exposure in patients with seasonal allergic asthma.² Cysteinyl leukotrienes have been shown to be involved in the activation and migration of eosinophils³ and dendritic cells⁴ to the bronchial

mucosa in response to allergen. Montelukast, a leukotriene receptor antagonist, has been shown to be effective in the treatment of chronic asthma and in relieving symptoms of seasonal allergic rhinitis^{5–7} but, to date, has not been specifically evaluated in the subpopulation of asthmatic patients with seasonal asthma symptoms and aeroallergen sensitivity. The goal of this study was to evaluate the treatment effect of montelukast vs placebo in this population. We evaluated whether montelukast would provide superior asthma symptom relief compared with placebo for 3 weeks of treatment during the allergy season.

METHODS

Patients

Institutional review boards at each study site approved the study protocol, and written informed consent was obtained from all patients before enrollment. Patients with at least a 1-year history of chronic asthma that was symptomatic during the allergy season and otherwise in good physical and mental health were eligible to participate in the study if they were 18 years or older and reported a predetermined level of asthma symptoms (32 points per week on a 0- to 6-point daily scale) and β -agonist use (≥ 1 puff daily) during the run-in period. In addition, patients were required to have a baseline forced expiratory volume in 1 second (FEV_1) of at least 60% of

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predicted, airway reversibility of at least 12% (as demonstrated by FEV₁ after inhaled β -agonist administration) at randomization or within the preceding year, and documented sensitivity to seasonal aeroallergens as demonstrated by a positive skin prick test reaction (wheal ≥ 3 mm greater than the saline control) to at least 2 geographically relevant seasonal aeroallergens at the first study visit or within the preceding year. Eligible patients had been nonsmokers for at least 1 year, with a smoking history of no more than 10 pack-years. Patients taking a stable dose of nasal cromolyn, nasal corticosteroids, or oral antihistamines for allergic rhinitis or maintenance doses of traditional immunotherapy were permitted to enter the study. Patients were excluded if they had taken oral, intravenous, intramuscular, or intra-articular corticosteroids within 1 month; inhaled corticosteroids, cromolyn, nedocromil, theophylline, or leukotriene receptor antagonists within 10 days; oral or long-acting inhaled β -agonists or inhaled anticholinergic agents within 10 days; or intravenous gamma globulin or immunosuppressants within 1 month. Patients who had been treated in an emergency department within 1 month, had been hospitalized for asthma within 3 months, or had unresolved symptoms and signs of an upper respiratory tract infection within 3 weeks of the first study visit or during the run-in period were excluded. Female patients who were pregnant or breastfeeding were not eligible to participate in the study.

Study Design

Protocol 289 was a randomized, double-blind, parallel-group study conducted under in-house blinding conditions at 69 study sites in the United States. The study compared the treatment effect of montelukast sodium (10 mg in the evening) vs placebo during the 2004 spring allergy season in adults with chronic asthma that is symptomatic during the allergy season and with relevant documented seasonal aeroallergen sensitivity. Rescue medication (albuterol) was allowed, as needed, throughout the study.

There was a 1-week, single-blind, placebo run-in period to evaluate inclusion criteria, to obtain baseline symptom scores and frequency of β -agonist use for analysis, and to evaluate patient competence in completing electronic diary entries and compliance with study medication. If the patient had been taking an asthma controller medication, this medication was discontinued at least 10 days before entering the run-in period. Patients must have had at least a 4-day run-in period to qualify for randomization. Patients whose asthma worsened during the prestudy washout or run-in period and who, in the opinion of the investigator, required prohibited therapy were excluded before randomization.

The run-in period was followed by a 3-week, double-blind treatment period during which patients received either oral montelukast (10 mg once nightly) or matching placebo. Eligible patients were randomly assigned to a treatment group according to a computer-generated allocation schedule. Clinic visits were scheduled at the beginning and end of the

3-week treatment period. During the treatment period, an electronic diary was used to collect information on daytime symptoms, nighttime symptoms, inhaled β -agonist use, and asthma attacks. Patients were asked to perform and record peak flow measurements twice daily: in the morning and in the evening before taking study medication. During this period, patients whose peak expiratory flow rate (PEFR) decreased below the predefined alert level (60% of the baseline value as determined at visit 2) or whose asthma symptoms worsened and, in the opinion of the investigator, required prohibited therapy were discontinued from the study.

Efficacy and Safety Analyses

The primary variable used to determine asthma control was change from baseline to week 3 in the daytime asthma symptom score. Daily scores were calculated as the average scores for 4 questions from a validated questionnaire regarding daytime asthma symptoms and activity limitations on a scale from 0 to 6: How often did you experience asthma symptoms today (0 = "none of the time" and 6 = "all of the time")? How much did your asthma symptoms bother you today (0 = "not at all bothered" and 6 = "severely bothered")? How much activity could you do today (0 = "more than usual activity" and 6 = "less than usual activity")? How often did your asthma affect your activities today (0 = "none of the time" and 6 = "all of the time")? Average scores for the baseline and treatment periods were calculated using all the daily scores in the period. Secondary end points included nighttime asthma symptoms, morning and evening PEFRs, inhaled β -agonist use, asthma attacks, and discontinuations due to asthma. An exploratory end point was the change in allergic rhinitis symptoms during the study as measured by an end-of-study global evaluation question completed by each patient: Compared with when I entered the study, my allergic rhinitis symptoms (ie, nasal itching, sneezing, runny nose, and nasal congestion) are now: 0 = "very much better," 1 = "moderately better," 2 = "a little better," 3 = "unchanged," 4 = "a little worse," 5 = "moderately worse," or 6 = "very much worse." In addition, responses were collapsed into categories: scores of 0, 1, 2 = "better," 3 = "no change," and 4, 5, 6 = "worse." The overall incidence of adverse experiences (AEs) and the incidence of any serious AEs, drug-related AEs, and AEs that caused discontinuation were collected to evaluate tolerability and safety.

Statistical Analyses

With 225 evaluable patients per group, the study provided 90% power to declare significance at the .05 level compared with placebo if the true difference between montelukast and placebo in daytime symptom score was -0.23 point and the SD was 0.75 point. The primary efficacy analysis of daytime asthma symptom scores used a modified intention-to-treat approach, including all randomized patients with at least 1 diary evaluation in each of the baseline and treatment periods. No missing values were imputed. The primary efficacy vari-

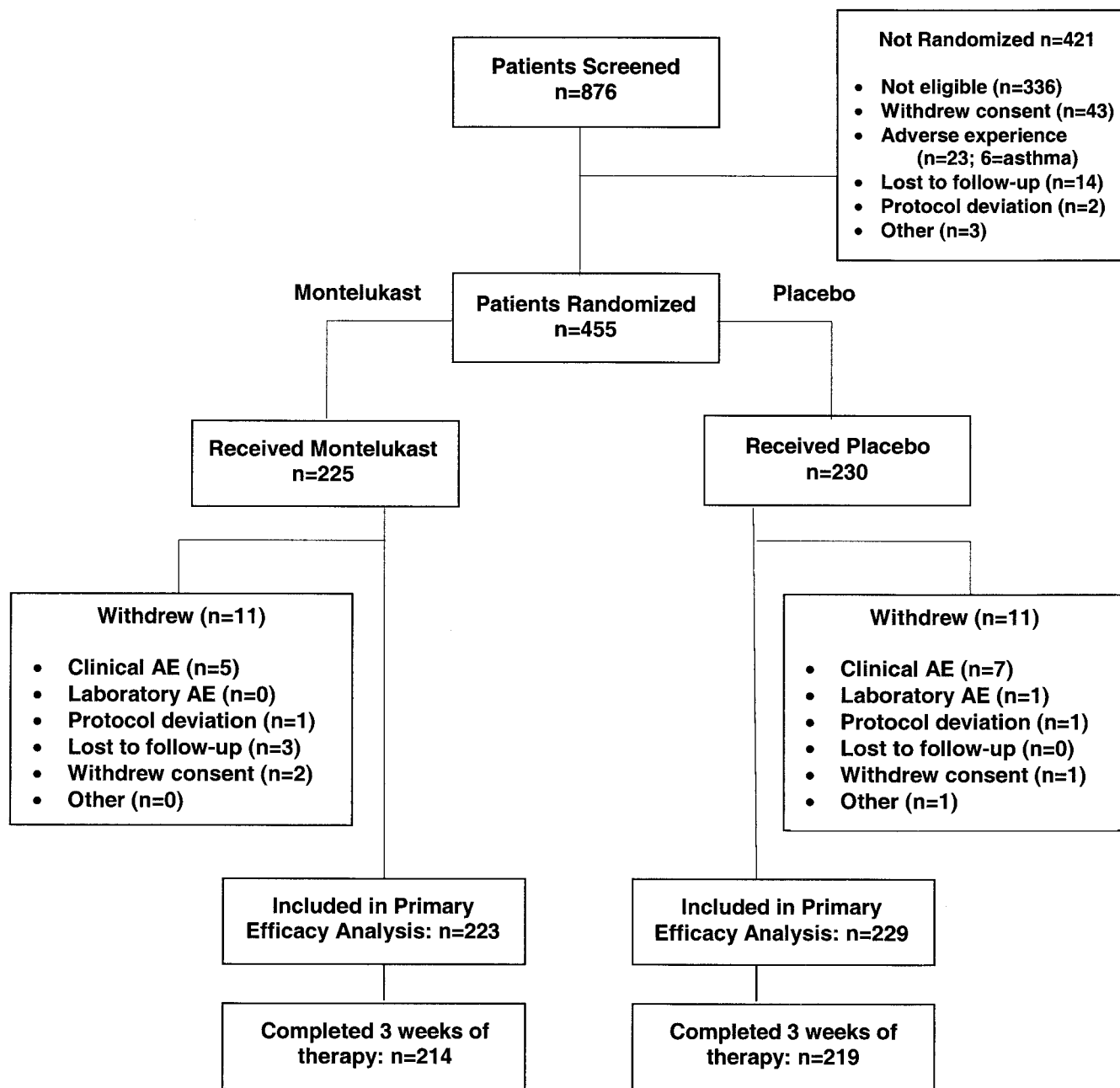


Figure 1. Patient accounting. AE indicates adverse experience.

able was evaluated using an analysis of covariance model with factors for study site, baseline daytime asthma symptom score, and treatment group. Analyses for other change (or percentage change) from baseline efficacy end points were performed using the same approach as the primary end point, with the baseline value of the end point as a covariate in the model. For the analysis of asthma attacks, the proportion of patients with asthma attacks was analyzed using a logistic regression model. For analysis of the

global allergic rhinitis evaluation, the data were analyzed using an analysis of variance model with treatment and study site as factors.

All randomized patients who received at least 1 dose of study medication were included in the safety analyses. The Fisher exact test was used to evaluate the incidence of clinical and laboratory AEs between treatment groups. The 95% confidence intervals for the differences in proportions were calculated using a method based on the Wilson score method.⁸

Table 1. Patient Demographics and Baseline Characteristics

Variable	Montelukast group (n = 225)	Placebo group (n = 230)
Age, mean (range), y	35.5 (18–66)	36.8 (18–76)
Female sex, %	72.4	67.8
Race, %		
White	80.0	82.6
Black	11.6	9.1
Hispanic	6.2	5.7
Other	2.2	2.6
History of allergic rhinitis, %	99.6	99.1
FEV ₁ , mean (SD), % predicted	83.3 (12.3)	82.2 (13.6)
Reversibility, mean (SD), %	19.8 (9.2)	20.7 (11.2)
Daytime symptom score, mean (SD)*	2.6 (0.8)	2.6 (0.8)
Nighttime symptom score, mean (SD)†	0.6 (0.5)	0.6 (0.5)
β-agonist use, mean (SD), puffs/d	3.1 (1.8)	3.0 (1.9)
Morning peak expiratory flow rate, mean (SD) L/min	366.7 (93.8)	367.0 (94.8)
Evening peak expiratory flow rate, mean (SD) L/min	370.5 (93.9)	374.1 (92.8)

Abbreviation: FEV₁, forced expiratory volume in 1 second.

* On a scale from 0 to 6.

† On a scale from 0 to 3.

RESULTS

Patients

A summary of patient accounting is shown in Figure 1. A total of 455 patients were randomly assigned to treatment in the study (225 received montelukast and 230 received placebo). Of these patients, 452 (99.3%) had at least 1 baseline and 1 treatment diary evaluation of the primary efficacy end point (daytime symptom score) and were included in the modified intention-to-treat population, and 433 patients (95.2%) completed the trial. Twenty-two patients (4.8%) discontinued the study for the reasons shown in Figure 1. The treatment groups were similar with respect to the percentage of patients who discontinued the study and the reasons for discontinuation.

Most patients were female (70.1%) and white (81.3%). Average patient age was 36.1 years. Nearly all of the patients reported a history of allergic rhinitis, and 90% (197 in the montelukast group and 213 in the placebo group) reported seasonal flare-up of rhinitis symptoms. The treatment groups were similar in terms of sex, age, and race and in all pranandomization asthma-associated measures (Table 1).

Efficacy

Daytime symptom score. Figure 2 shows the mean change from baseline in the daytime asthma symptom score for each treatment group during the 3 weeks of treatment, with a lower score representing an improvement in asthma symptoms. Compared with placebo, the montelukast group demonstrated a significant improvement in daytime asthma symptom score

change from baseline (least squares mean difference, -0.20 ; 95% confidence interval, -0.34 to -0.07 ; $P = .002$).

Secondary asthma end points. Compared with the placebo group, the montelukast group used significantly less β-agonist, had significantly fewer nighttime asthma symptoms, and had significantly greater improvement in PEFr during the 3 weeks of treatment (Table 2).

Global evaluation of allergic rhinitis. A prespecified exploratory analysis included all patients who had active (within the 3 weeks before randomization) allergic rhinitis symptoms as determined by the investigator. Of 455 randomized patients, 423 met this criterion. Figure 3 shows the mean scores from the allergic rhinitis question answered at the end of the treatment period, with a lower score representing more improvement in allergic rhinitis symptoms. The improvement in global allergic rhinitis symptoms with montelukast was greater than that with placebo (least squares mean difference = -0.25 ; 95% confidence interval, -0.50 to 0.00 ; $P = .054$). A further exploratory analysis was performed to determine whether the reported improvement in allergic rhinitis symptoms correlated with improvement in the asthma symptom score. For the montelukast and placebo groups, patients reporting greater improvement in daytime asthma symptoms also reported greater improvement in allergic rhinitis symptoms (Fig 4). Of note, 128 patients (30.3%) were taking concomitant allergic rhinitis medications: 35 (17 in the montelukast group and 18 in the placebo group) were taking nasal corticosteroids, 97 (44 in the montelukast group and 53 in the placebo group) were taking systemic antihistamines, and 42 (25 in the montelukast group and 17 in the placebo group) were taking nasal preparations of antihistamines or decongestants (some patients were taking medications from more than 1 of these categories). Allergic rhinitis medication use was distributed similarly between treatment groups, however, and a subsequent subgroup analysis yielded no significant interaction between treatment and allergic rhinitis medication use (interaction $P = .506$).

Asthma attacks. Asthma attacks were analyzed as the proportion of patients with any asthma attack during the 3 weeks of treatment. An asthma attack was defined as an unscheduled visit to the physician's office, an emergency department visit, a hospitalization, or treatment with oral, intravenous, or intramuscular corticosteroids as recorded on the diary. The percentage of patients with any asthma attack was 2.2% (5/224) in the montelukast group and 1.7% (4/229) in the placebo group; this difference was not statistically significant.

Discontinuation due to asthma. Study discontinuation due to asthma was analyzed as the proportion of patients who (1) had an AE of asthma that caused discontinuation, (2) had an AE other than asthma that caused discontinuation but also had an AE of asthma, or (3) took a prohibited asthma medication, resulting in a reason for discontinuation of "patient withdrew" or "protocol deviation." The percentage of patients who discontinued because of asthma was 1.3% (3/225) in the montelukast group and 3.0% (7/230) in the placebo

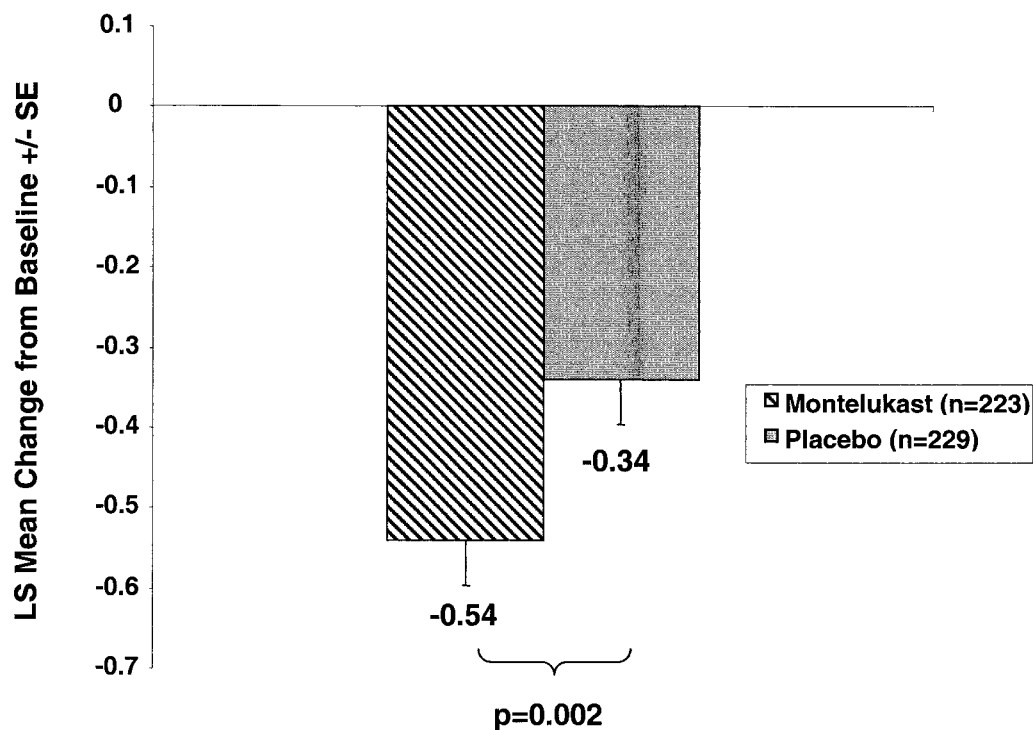


Figure 2. Least squares (LS) mean change from baseline in daytime asthma symptom scores for the montelukast and placebo groups. A lower score represents an improvement in daytime symptom scores.

Table 2. Additional Efficacy Measures

End point	Montelukast		Placebo		Treatment difference (95% CI) (montelukast – placebo)	P value‡
	Baseline value*	Change from baseline†	Baseline value*	Change from baseline†		
β-agonist use, puffs/d§	3.1 (1.8)	−0.8 (−1.0 to −0.6)	3.0 (1.9)	−0.4 (−0.6 to −0.2)	−0.4 (−0.7 to −0.1)	.003
Nighttime symptom score§	0.60 (0.48)	−0.17 (−0.22 to −0.12)	0.63 (0.49)	−0.07 (−0.12 to −0.02)	−0.10 (−0.16 to −0.04)	<.001
Morning peak flow, L/min¶	365.5 (93.2)	17.2 (11.3 to 23.1)	367.7 (94.5)	1.3 (−4.4 to 7.0)	15.9 (8.7 to 23.1)	<.001
Evening peak flow, L/min¶	370.7 (93.7)	11.3 (5.5 to 17.1)	374.1 (93.1)	−2.0 (−7.7 to 3.6)	13.3 (6.1 to 20.5)	<.001

Abbreviation: CI, confidence interval.

* Observed mean (SD).

† Adjusted mean change from baseline and treatment differences (95% CI) from the analysis of covariance model with effects for treatment, study site, and baseline value.

‡ No adjustment for multiple tests was made.

§ A negative change from baseline indicates a favorable outcome.

¶ A positive change from baseline indicates a favorable outcome.

group. There was no significant difference between the montelukast and placebo groups in terms of the proportion of patients who discontinued study participation because of asthma. Of the 10 patients who discontinued because of asthma, 8 did not indicate in the diary that they had any unscheduled visits to the physician's office, emergency department visits, hospitalizations, or corticosteroid use; thus,

they were not counted as having an asthma attack in the analysis of asthma attacks.

Safety

All but 1 of the 455 randomized patients were included in the safety analysis: 1 patient did not receive study medication and was excluded. The montelukast and placebo groups were

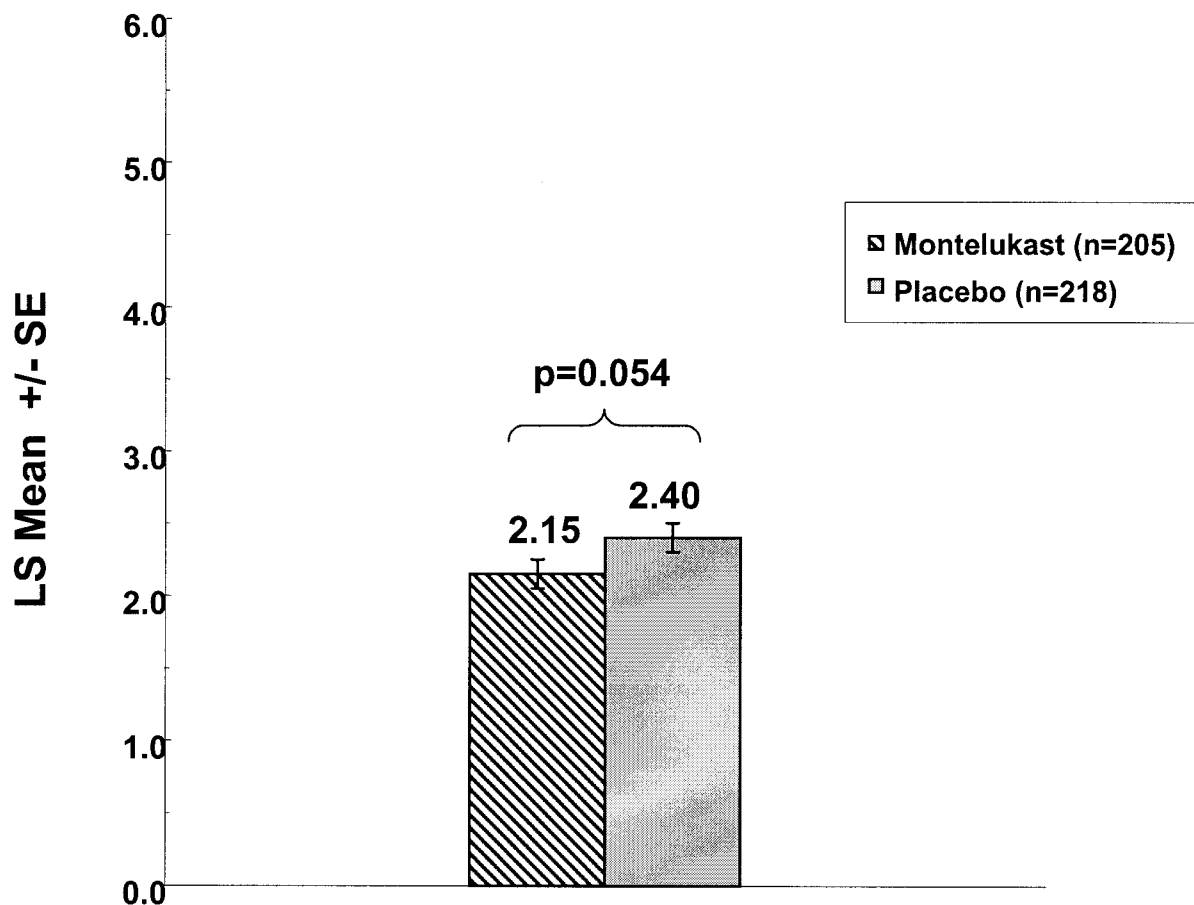


Figure 3. Least squares (LS) mean score on the global allergic rhinitis question answered at the end of the treatment period for the montelukast and placebo groups. A lower score represents an improvement in allergic rhinitis symptoms since the beginning of the study.

comparable in the proportion of patients with clinical and laboratory AEs. Five patients (2.2%) receiving montelukast and 7 (3.0%) receiving placebo discontinued study participation because of a clinical AE. None of the discontinuations was considered to be drug related by the investigator.

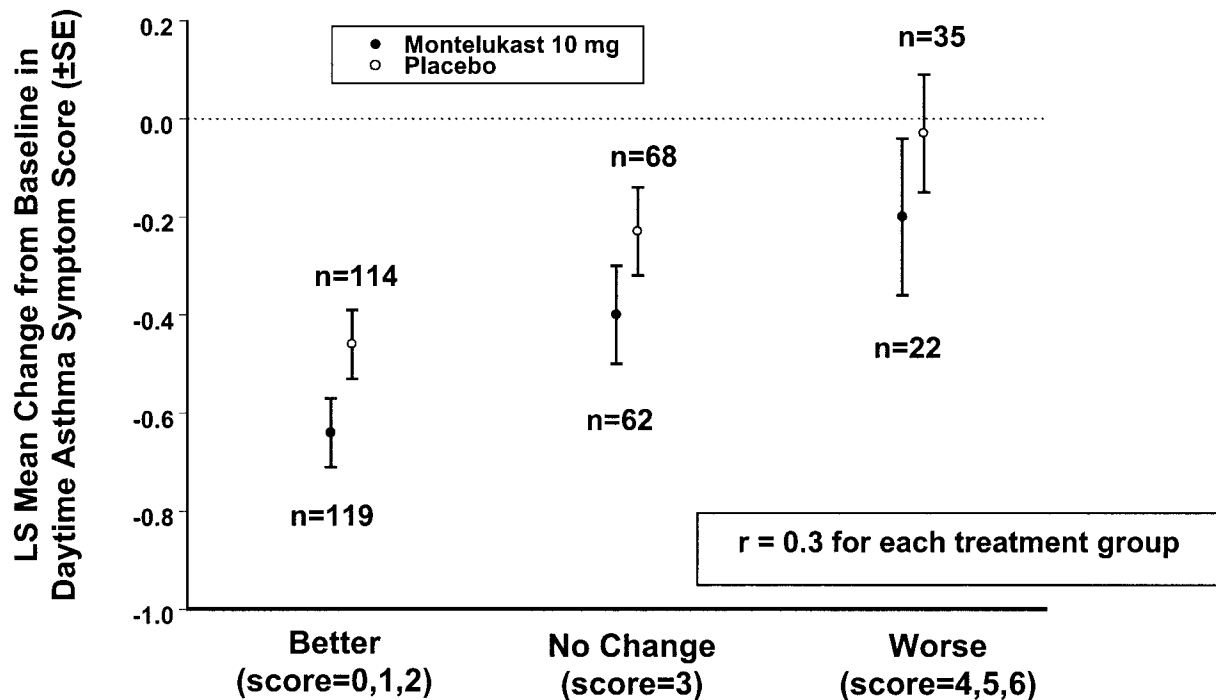
DISCUSSION

The goal of the present study was to determine whether montelukast, a leukotriene receptor antagonist, would provide relief of asthma symptoms during the allergy season in the subpopulation of asthma patients with seasonal aeroallergen sensitivity. The results showed that treatment with montelukast was superior to placebo on all asthma outcome measures for the 3-week treatment period during the spring allergy season. There were no differences between treatment groups in number of asthma attacks or asthma-related discontinuation rates, which was not unexpected given the rarity of these events during the study's short duration and the generally mild asthma population.

Allergic sensitization is prevalent among children and adults with asthma, occurring in 70% to 80% of patients.⁹⁻¹¹

Previous clinical trials have examined the efficacy of other asthma controller medications on decreasing or preventing airway hyperresponsiveness and symptoms in patients with allergic asthma during the allergy season,¹²⁻¹⁶ including other leukotriene receptor antagonists,¹⁷ but none have looked at the efficacy of montelukast in these patients. Studies^{18,19} have shown that montelukast attenuates the early and late asthmatic responses to allergen challenge, as measured by FEV₁, and methacholine responsiveness, but no previous studies have been performed with natural allergen exposure during the allergy season.

It has been shown that congestion or inflammation in the upper airway can adversely affect lower airway function. There are several hypotheses to explain this, including (1) that nasal congestion may lead to mouth breathing, with increased allergen deposition into the lungs and reduced warming/humidification of inspired air, (2) that upper airway inflammation leading to systemic absorption of mediators may trigger asthma symptoms, and (3) that there is a neurogenic bronchoconstrictive reflex linking the upper and lower airways.²⁰⁻²⁴ Treating nasal congestion has been shown to



Global Allergic Rhinitis Category

Figure 4. Least squares (LS) mean change from baseline in daytime asthma symptom scores for each treatment group by global allergic rhinitis category for the montelukast and placebo groups.

improve asthma symptoms in patients with allergic rhinitis who also had asthma.^{25,26}

At the end of the study, patients with active symptoms of allergic rhinitis at baseline were asked whether their rhinitis symptoms had improved, worsened, or remained the same. All but 3 of the patients enrolled in the study reported a history of allergic rhinitis, with 90% of these reporting seasonal flare-ups, consistent with other studies that found that approximately 90% of patients with seasonal allergic asthma also experience allergic rhinitis.²⁷ For these patients, montelukast provided a greater improvement in the global allergic rhinitis symptom score than placebo.

A potential confounding factor in the analyses of daytime asthma symptom scores and global allergic rhinitis scores was that several patients (30%) were taking allergic rhinitis medications concomitantly, potentially affecting patients' ability to detect an improvement in asthma symptoms or further improvement in rhinitis symptoms due to study treatment. Previous studies have assessed the effect of montelukast plus antihistamines on seasonal allergic rhinitis^{28–31} and asthma^{32,33} and found that combination therapy was effective at decreasing or preventing symptoms of both conditions. Also, use of antihistamines alone results in bronchodilation,^{34,35} potentially improving the asthma symptom scores in patients in the placebo group taking this class of concom-

itant allergic rhinitis medication. Allergic rhinitis medication use was distributed similarly between treatment groups, however, and no significant interaction between treatment and allergic rhinitis medication use was detected.

The large population of study patients with a history of allergic rhinitis allowed for evaluation of the correlation between changes in asthma and allergic rhinitis symptoms, an important clinical issue. Exploratory analyses showed a positive correlation between patient-reported changes in asthma and allergic rhinitis symptoms. This result is similar to that shown by Bousquet et al³⁶ in their retrospective analysis of characteristics of patients with seasonal allergic rhinitis and concomitant asthma. However, the present study was not designed or powered to fully explore the link between improvement in rhinitis symptoms and improvement in asthma symptoms. Thus, further studies that prospectively examine improvements in multiple variables of allergic rhinitis and asthma in patients with concomitant disease are needed. Nonetheless, the correlation between improvements in asthma scores and rhinitis scores (Fig 4) supports the relationship between the upper and lower airways and a potential benefit in treatment modalities that can positively affect both diseases concomitantly.

A limitation of this study is that the study population had generally mild asthma, so the applicability of the results to

other asthma populations is uncertain. Conclusions are based primarily on patient-reported measures of symptom relief, rescue treatment, and PEFs because spirometric pulmonary function assessments were not obtained. However, recent clinical trials in asthma have been placing more emphasis on evaluating treatment efficacy by effects on clinical outcomes, including reduction of rescue β -agonist use, rather than on FEV₁; the present study design is in keeping with this move toward evaluation of symptom relief as the primary objective.

In summary, montelukast provided significant improvement in asthma control during a 3-week treatment period during the allergy season compared with placebo in patients with chronic asthma and seasonal aeroallergen sensitivity. These results are consistent with those of other studies showing montelukast to be effective in the treatment of chronic asthma but extend those findings by evaluating the important subpopulation of asthmatic patients with seasonal aeroallergen sensitivity. Furthermore, the positive trends in improvement of rhinitis and asthma in the same patients are worthy of further study. These results affirm that montelukast is an effective and well-tolerated therapeutic option for these patients.

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