

Original article

Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period

Background: Proinflammatory mediators such as the cysteinyl leukotrienes are important in the pathophysiology of allergic rhinitis. This study evaluated the efficacy and tolerability of montelukast, a cysteinyl leukotriene receptor antagonist, given once daily in the morning for treatment of seasonal (fall) allergic rhinitis for 4 weeks.

Methods: This was a randomized, double-blind trial with a placebo run-in and a 4-week treatment period. Patients ($n = 1079$) with a history of allergic rhinitis and a positive skin test to seasonal pollen allergens were assigned to placebo, montelukast 10 mg, or loratadine 10 mg. Symptoms were assessed with a daily diary.

Results: Montelukast was more effective than placebo in improving scores for the primary endpoint of daytime nasal symptoms ($P = 0.003$) and the secondary endpoints of night-time, composite, and daytime eye symptoms, patient's and physician's global evaluations of allergic rhinitis, and rhinoconjunctivitis quality-of-life ($P \leq 0.006$). The positive control loratadine also improved scores for the primary endpoint ($P \leq 0.001$) and the majority of the secondary endpoints ($P < 0.03$). When analyzed by week, the treatment effect of montelukast was more persistent than loratadine over all 4 weeks of treatment.

Conclusion: Montelukast provided effective relief of seasonal allergic rhinitis symptoms when given once daily in the morning, showed significant and sustained improvement in symptoms of allergic rhinitis over 4 weeks of treatment, and was well-tolerated.

**J. van Adelsberg¹, G. Philip¹,
A. J. Pedinoff², E. O. Meltzer³,
P. H. Ratner⁴, J. Menten¹, T. F. Reiss¹
for the Montelukast Fall Rhinitis
Study Group**

¹Merck Research Laboratories, Rahway, NJ;

²Princeton Center for Clinical Research, Princeton, NJ; ³Allergy & Asthma Medical Group and Research Center, A.P.C., San Diego, CA; ⁴Sylva Research, San Antonio, TX, USA

Key words: leukotriene antagonist; montelukast; seasonal allergic rhinitis; weekly rhinitis symptoms scores.

Janet van Adelsberg, MD
126 E. Lincoln Ave
P.O. Box 2000, RY34B-336
Rahway, NJ 07065-0900, USA

Accepted for publication 24 March 2003

Allergic rhinitis is the most common form of allergic disease, estimated to affect up to 20% of the population worldwide (1). This disorder is an inflammatory disease of the airways and shares with asthma a number of common epidemiologic, histologic and pathophysiologic features (2–4). These include the high numbers of inflammatory cells such as mast cells and eosinophils in the airway; when activated on exposure to airborne allergens they undergo degranulation and release inflammatory substances, including cysteinyl leukotrienes, histamine, prostaglandin D₂, and kinins.

The cysteinyl leukotriene type-1 (CysLT₁) receptor antagonist montelukast, administered once daily in the evening, has been documented to significantly improve symptoms of seasonal allergic rhinitis (5–7). As montelukast provides relief of symptoms for 24 h and its pharmacokinetic profile is similar whether dosed in the morning or evening (8), we predicted that montelukast would provide benefit in seasonal allergic rhinitis regardless of the time of dosing. Therefore, the primary objective of this study was to test the efficacy of montelukast 10 mg administered once daily in the morning to patients with seasonal allergic rhinitis.

Few studies have examined the treatment of seasonal allergic rhinitis with oral agents for periods longer than 2 weeks (9, 10). These studies of antihistamines, with or without decongestants, did not specifically examine the time course of treatment effect by week. However, their results are suggestive of a diminishing treatment effect on seasonal allergic rhinitis symptoms over time. While one possible explanation could be that symptoms scores and hence treatment effect size decreases as pollen counts decline during the course of the study, an alternative explanation is that histamine plays a major role in the early but not the evolved inflammatory response in seasonal allergic rhinitis. Because cysteinyl leukotrienes play a role in the late phase of the allergic response (11), we reasoned that the time course of the treatment effect of montelukast might differ from that of the antihistamines. Accordingly, a second objective of this study was to examine the effect of montelukast on the symptoms of seasonal allergic rhinitis during a 4-week treatment period.

This paper reports the results of a multicenter, double-blind, randomized, parallel-group, placebo-controlled study on the effects of montelukast 10 mg given once

daily in the morning on the symptoms of seasonal allergic rhinitis during a 4-week treatment period. Loratadine, an antihistamine, served as the positive control to validate the study. The results show that montelukast provided efficacy in daytime and night-time symptoms of seasonal allergic rhinitis with morning dosing with a durable and consistent treatment effect over the entire 4 weeks of the study.

Material and methods

This study was performed during the fall pollen season in 47 study centers in the United States. The study was conducted in accordance with applicable statutes and regulations regarding the protection of patients' rights and welfare and was approved by Institutional Review Boards at each study site. All patients gave written informed consent before any study procedure was performed.

Study design and patients

There were two study periods: a 3–5-day single-blind, placebo run-in period followed by a 4-week, double-blind treatment period. Patients were randomized in a 5 : 2 : 5 ratio to montelukast 10 mg, loratadine 10 mg, or placebo treatment groups, respectively. All study medications were administered once daily in the morning. Blinding was ensured by including matching-image placebo tablets. Patients were to complete the study within the fall pollen season, determined by historical pollen counts in their locality.

Patients were nonsmoking adolescents and adults, ages 15–82 years, who were symptomatic during the fall and had at least a 2-year history of seasonal allergic rhinitis. Eligible patients exceeded a defined minimum daytime nasal symptoms score during the placebo run-in period. Prior to randomization and enrollment into the double-blind treatment period, patients had to demonstrate a positive skin test to a fall allergen. The allergens identified by the study sites as the most prevalent fall seasonal allergens found in their areas are listed in Table 1. Each site selected six allergens from this list for skin testing. Kits containing the selected antigens were provided to each study site. Skin testing was performed during Visit 1. Test solutions were applied to the inner forearm by skin pricks. A wheal larger than that of the saline control by at least 3 mm was considered positive. The percentages of patients showing a positive or negative response of the skin test to each allergen are also shown in Table 1.

Patients with mild asthma, using only short-acting β -agonist bronchodilators, were allowed to participate. Patients with the following conditions were excluded: perennial rhinitis with little or no seasonal flare-ups; rhinitis medicamentosa; nonallergic rhinitis; structural nasal obstruction; upper respiratory tract infection; acute or chronic pulmonary disorder. Medications for allergic rhinitis and conjunctivitis were not allowed during the study. Medications that could affect nasal or ocular symptoms, including decongestants and anti-inflammatory drugs, and oral or long-acting inhaled β -agonists, theophylline, and leukotriene modifiers were also excluded. Patients who had begun immunotherapy within the previous 6 months were excluded.

Efficacy assessments

All patients completed a daily diary during the run-in and treatment periods, as described previously (5–7). The primary

Table 1. Pollen allergens and patient sensitivity

Pollen allergen (antigen)*	Skin test results†		Total no. patients tested‡
	% of patients testing positive	% of patients testing negative	
Cocklebur	37.4	62.6	516
Dock, yellow	34.9	65.1	169
Elm, cedar	48.9	51.1	319
English plantain	63.2	36.8	562
Goldenrod	45.5	54.5	189
Kochia	43.4	56.6	159
Lamb's quarters	43.9	56.1	754
Marsh elder, burweed	33.8	66.2	74
Marsh elder, rough	37.4	62.6	334
Pigweed, rough	51.0	49.1	687
Pigweed, spiny	55.5	44.5	155
Ragweed, short	15.3	84.8	1036
Ragweed, tall	23.7	76.3	857
Russian thistle	34.4	65.6	349
Sagebrush	33.7	66.3	196
Sheep sorrel	48.3	51.7	87

* Lists the allergens identified by the study sites as the most prevalent fall seasonal allergens found in their areas.

† Skin testing for antigen reactivity is described under Materials and methods.

‡ Because each site selected six allergens from the 16 possible antigens, not all patients were tested for each antigen.

endpoint was daytime nasal symptoms score, an average of the individual symptoms of nasal congestion, rhinorrhea, pruritus, and sneezing. Secondary endpoints included night-time symptoms score (average of the individual symptoms of difficulty going to sleep, night-time awakenings, and nasal congestion on awakening), and daytime eye symptoms score (average of the individual symptoms of tearing, pruritus, redness, and puffiness). Each individual symptom was rated on a 4-point scale: 0, none; 1, mild; 2, moderate and 3, severe.

Other secondary endpoints were the composite symptoms score (average of the daytime nasal symptoms score and night-time symptoms score), patient's global evaluation, physician's global evaluation, and rhinoconjunctivitis quality-of-life score (average of seven domains: activity, sleep, non-nose/noneye symptoms, practical problems, nasal symptoms, eye symptoms, and emotions). Patients and investigators each provided a global evaluation of allergic rhinitis at the end of 2 weeks of treatment (7). The physician's global evaluation was based on the patient's oral history and physical examination without reference to the patient's daily diaries. Patients completed a rhinoconjunctivitis quality-of-life questionnaire (12, 13) before randomization and at the end of 2 and 4 weeks of treatment or upon discontinuation.

Patients also recorded the exploratory endpoints of morning (end-of-dosing interval) nasal symptoms score and eye symptoms score on the same 4-point diary scale, using instantaneous recall on arising in the morning, before the next dose of study medication.

Other measurements

Peripheral blood eosinophil counts were measured before and at the end of the 4-week treatment period. Airborne weed pollens were collected using a Rotorod® sampler (Multidata LLC, St Louis Park, MN) and were analyzed by Multidata LLC.

Safety assessments

Safety and tolerability were assessed by adverse events monitoring, physical examinations, and laboratory examinations [hematology, serum biochemistry, and urinalysis; Covance Central Laboratory Services, Inc. (Indianapolis, IN)].

Statistical analysis

Efficacy analyses for all endpoints employed an intention-to-treat approach that included all randomized patients who had a baseline and at least one post-treatment symptom assessment. Mean symptom scores were calculated at baseline (average of daily scores during the placebo run-in period), during the first 2 weeks of treatment (average of daily scores during the first 2 weeks of the double-blind treatment period), during all 4 weeks of treatment (average of daily scores during the 4-week double-blind treatment period), and after 1, 2, 3 and 4 weeks of treatment (average of daily scores during each week of the double-blind treatment period). Changes from baseline were analyzed by subtracting the mean score during treatment from the baseline score. The first 2 weeks of the active treatment period was prespecified as the primary analysis timepoint. For the change from baseline, treatment comparisons were based on testing specific pairwise contrasts using an analysis of covariance (ANCOVA) model, with factors for treatment and study centers and using the baseline value of the dependent variable as a covariate. Treatment differences were estimated by least-squares (LS) means obtained from the ANCOVA model. The mean treatment difference between the montelukast and loratadine treatment groups

was estimated using 95% confidence intervals. An analysis of variance model (ANOVA), with terms for treatment and study center, was used to analyze global evaluations. To explore the change over time in treatment effect, a slope analysis of the weekly symptoms scores over the 4-week treatment period was performed using a mixed-model approach. For this analysis, the time effect was modeled by an intercept and slope for each treatment group. To model the influence of decreasing pollen counts during the study, the patient-specific change from baseline in weed pollen count was included in the model as a fixed effect for each treatment period week. Regional differences were modeled by including a fixed study center effect in the model and patient-specific effects were included as a random slope and intercept for each patient. Time effects were assessed by the difference in slopes between montelukast and placebo and between loratadine and placebo.

Based on the results of previous study protocols, it was estimated that if there were 360 patients in each of the montelukast and placebo groups, the study would have a 90% power to detect a 0.13 difference in change from baseline in daytime nasal symptoms score between the two treatments at 2 weeks. Similarly, the study was designed such that if there were 136 patients in the loratadine group and 360 patients in the placebo group, the study would have an 80% power to detect a 0.15 difference in change from baseline in daytime nasal symptoms score between the two treatment groups. The study was powered for the comparisons of each of the active treatments with placebo. The difference in treatment effects between montelukast and loratadine was expected to be smaller than the treatment effect of each active treatment compared with placebo. Consequently, the study is not adequately powered for the direct comparison between montelukast and loratadine and no formal testing was performed.

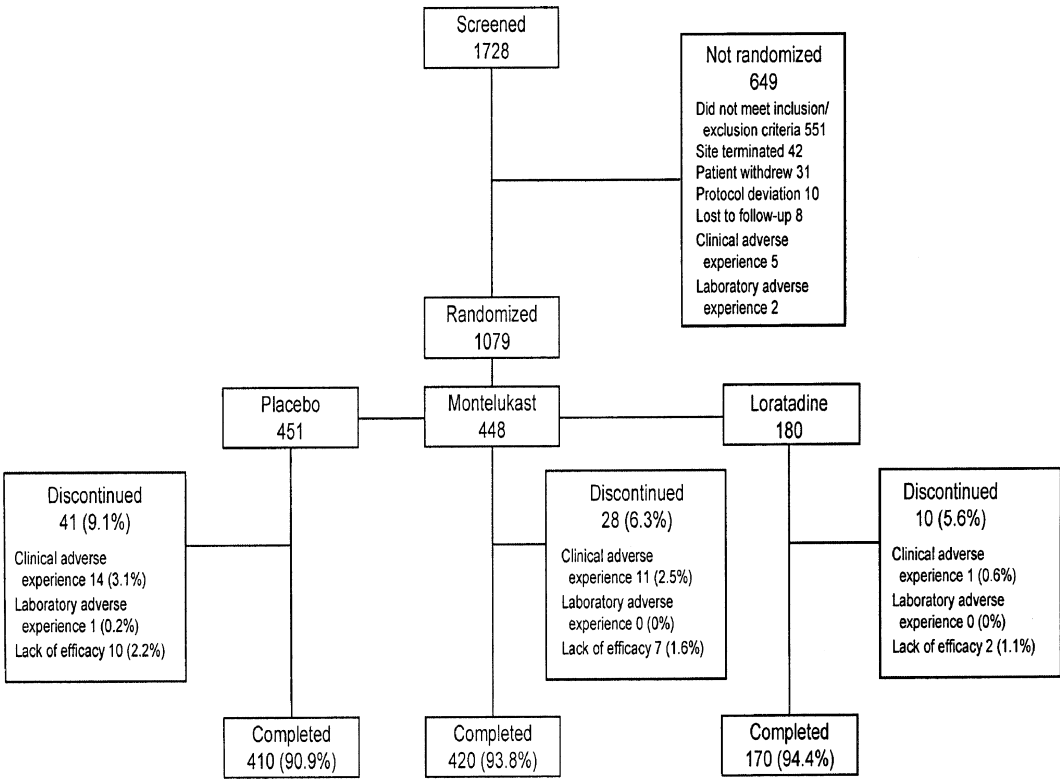


Figure 1. Patient disposition. All percentages represent the percent of patients randomized into the indicated treatment group.

Results

Baseline characteristics

Of 1728 patients screened, 1079 patients were randomized and 1000 (93%) completed the study. Six hundred and forty-nine patients were excluded during screening (Fig. 1). About two-thirds of the enrolled patients were women (67%); most were white (82%) and in the age range of 18–64 years (91%); 89% had a history of allergic conjunctivitis; 23% had a history of asthma, with 6% reporting active symptoms of asthma (Table 2). There were no clinically meaningful differences among the treatment groups in any baseline characteristic, including baseline symptoms scores, secondary diagnoses, and concomitant drug therapies.

Endpoints

Montelukast, averaged over the primary analysis period of the first 2 weeks, was significantly more beneficial than placebo for the primary endpoint of daytime nasal symptoms score ($P = 0.003$) and the secondary endpoints of night-time symptoms score, composite symptoms score, daytime eye symptoms score, patient's global evaluation and physician's global evaluation ($P = 0.006$

for all secondary endpoints; Table 3). Montelukast provided significant benefit, relative to placebo, in the exploratory endpoint of morning (end-of-dosing interval) nasal symptoms score. There was a borderline significant effect ($P = 0.085$) on the instantaneous score for morning (end-of-dosing interval) eye symptoms averaged over the first 2 weeks of treatment. The primary and secondary endpoints showed significant improvement with montelukast relative to placebo over the entire 4 weeks of treatment ($P = 0.006$ for all primary and secondary endpoints; Table 3).

Montelukast was significantly different from placebo in three of four individual daytime nasal symptoms and all three individual night-time symptoms over the first 2 weeks as well as during all 4 weeks (Fig. 2). Patient responses on the rhinoconjunctivitis quality-of-life questionnaire showed significant improvements ($P < 0.03$, data not shown) from baseline for all seven individual quality-of-life domains during the first 2 weeks of treatment, and, except for the emotions domain where there was borderline significance ($P = 0.059$), during all 4 weeks. Montelukast significantly reduced blood eosinophil counts ($P = 0.002$) compared with placebo (Table 3).

Loratadine, the positive control, significantly improved the symptoms scores for the primary and secondary

Table 2. Patient baseline characteristics

Patient characteristics	Treatment groups		
	Placebo ($n = 521$)	Montelukast ($n = 522$)	Loratadine ($n = 171$)
Demographics			
Age, years (range)	36 ± 12 (15–82)	36 ± 13 (15–82)	39 ± 13 (15–79)
Sex, n (%)			
Male	150 (33)	147 (33)	61 (34)
Female	301 (67)	301 (67)	119 (66)
Race, n (%)			
White	378 (84)	365 (82)	145 (81)
Black	36 (8)	42 (9)	23 (13)
Hispanic	25 (6)	23 (5)	4 (2)
Other	12 (3)	18 (4)	8 (4)
Allergic history			
Duration of allergic rhinitis (years)	20 ± 12	19 ± 12	21 ± 13
History of allergic conjunctivitis, n (%)	397 (88)	400 (89)	162 (90)
History of asthma, n (%)	108 (24)	98 (22)	43 (24)
Recent asthma symptoms*, n (%)	29 (7)	23 (5)	13 (7)
Baseline efficacy measures			
Daytime nasal symptoms score†	2.16 ± 0.44	2.20 ± 0.46	2.23 ± 0.44
Night-time symptoms score†	1.65 ± 0.64	1.69 ± 0.64	1.77 ± 0.63
Composite symptoms score‡	1.94 ± 0.46	1.98 ± 0.47	2.03 ± 0.46
Daytime eye symptoms score†	1.61 ± 0.81	1.64 ± 0.73	1.64 ± 0.78
Rhinoconjunctivitis quality-of-life score§	3.37 ± 1.02	3.41 ± 1.00	3.46 ± 1.08
Peripheral blood eosinophil count ($\times 10^3$ cells/ μ l)	0.18 ± 0.12	0.19 ± 0.13	0.17 ± 0.11

* Presence of asthma symptoms (not further specified) at start of study, as noted by the patient.

† Mean score during placebo run-in period; all symptoms scored on 0 (best) to 3 (worst) scale.

‡ Mean of the daytime nasal symptoms score and the night-time symptoms score.

§ Mean of seven domains scored on 0 (best) to 6 (worst) scale.

Unless otherwise specified, values are mean ± SD.

Table 3. Results for montelukast vs placebo

Endpoint	Duration of treatment (weeks)*	LS mean change from baseline † (95% CI)		LS mean difference (95% CI)	P value
		Placebo	Montelukast		
Daytime nasal symptoms score	2	−0.23 (−0.28, −0.18)	−0.33 (−0.37, −0.28)	−0.10 (−0.16, −0.03)	0.003
	4	−0.33 (−0.38, −0.28)	−0.43 (−0.48, −0.38)	−0.10 (−0.17, −0.04)	0.003
Night-time symptoms score	2	−0.18 (−0.23, −0.14)	−0.28 (−0.32, −0.23)	−0.10 (−0.16, −0.04)	0.002
	4	−0.26 (−0.31, −0.22)	−0.36 (−0.40, −0.32)	−0.09 (−0.15, −0.03)	0.002
Composite symptoms score‡	2	−0.21 (−0.25, −0.16)	−0.30 (−0.35, −0.26)	−0.10 (−0.16, −0.04)	≤0.001
	4	−0.30 (−0.34, −0.26)	−0.40 (−0.45, −0.36)	−0.10 (−0.16, −0.04)	≤0.001
Daytime eye symptoms score	2	−0.18 (−0.23, −0.14)	−0.28 (−0.33, −0.23)	−0.10 (−0.16, −0.03)	0.006
	4	−0.27 (−0.32, −0.22)	−0.37 (−0.42, −0.31)	−0.10 (−0.17, −0.03)	0.006
Patient's global evaluation§	2	2.73 (2.59,2.88)	2.43 (2.29,2.57)	−0.30 (−0.50, −0.11)	0.002
Physician's global evaluation§	2	2.75 (2.62,2.88)	2.36 (2.23,2.50)	−0.39 (−0.57, −0.21)	≤0.001
Rhinoconjunctivitis quality-of-life¶	2	−0.55 (−0.65, −0.45)	−0.85 (−0.94, −0.75)	−0.30 (−0.43, −0.17)	≤0.001
	4	−0.85 (−0.96, −0.74)	−1.12 (−1.23, −1.01)	−0.27 (−0.42, −0.12)	≤0.001
Morning (end-of-dosing) nasal symptoms score	2	−0.20 (−0.25, −0.15)	−0.27 (−0.32, −0.22)	−0.07 (−0.13, −0.01)	0.034
	4	−0.28 (−0.33, −0.23)	−0.36 (−0.41, −0.32)	−0.08 (−0.15, −0.01)	0.016
Morning (end-of-dosing) eye symptoms score	2	−0.19 (−0.24, −0.14)	−0.25 (−0.30, −0.20)	−0.06 (−0.13, −0.01)	0.085
	4	−0.28 (−0.33, −0.23)	−0.33 (−0.38, −0.28)	−0.05 (−0.12, 0.02)	0.131
Eosinophil count (×10 ³ cells/μL)	4	0.01 (−0.00,0.02)	−0.01 (−0.02, −0.00)	−0.02 (−0.03, −0.01)	0.002

* Mean score during the first 2 weeks or all 4 weeks of treatment.

† Mean score during the first 2 or all 4-week blinded treatment period minus mean score during 3–5-day placebo run-in period.

‡ Mean of the daytime nasal symptoms score and the night-time symptoms score.

§ Values for global evaluations are absolute scores because this question was asked only at week 2.

¶ Mean of seven rhinoconjunctivitis quality-of-Life domains scored on 0 (best) to 6 (worst) scale.

LS, Least squares; CI, confidence interval. P value is for the comparison with placebo.

All symptoms were scored on 0 (best) to 3 (worst) scale; rhinoconjunctivitis quality-of-Life questions and global evaluations scored on 0 (best) to 6 (worst) scale.

endpoints over the first 2 weeks ($P \leq 0.03$) and all 4 weeks ($P \leq 0.03$) (Table 4), except for night-time symptoms, where loratadine provided no significant benefit [Fig. 2 (4-week data)]. The estimates of the differences between the two active treatments favored montelukast for eosinophil counts and favored loratadine for daytime nasal symptoms score for the first 2 weeks. The confidence intervals for the estimates of treatment differences for other endpoints included zero.

When examined by week, montelukast was significantly more effective than placebo in improving daytime nasal, night-time, daytime eye, and composite symptoms scores at every week (Fig. 3). In contrast, the treatment effect of loratadine by week, compared with placebo, tended to decrease throughout the study. To evaluate the time course of the treatment effect, an analysis of the slope of the mean change from baseline by week was performed for all 4 weeks. The difference in slopes between montelukast and placebo was $-0.01/\text{week}$ for each of the daytime, night-time, daytime eye, and composite symptoms scores, and was not significant, indicating a constant treatment effect greater than the placebo effect. In contrast, the difference in slopes between loratadine and placebo for the secondary endpoints ranged from 0.01 to $0.03/\text{week}$ ($P = \text{not significant}$) and was $0.04/\text{week}$ for the primary endpoint of daytime nasal symptoms score

($P = 0.036$), indicating a diminishing loratadine treatment effect for the primary endpoint. The prespecified analysis included pollen counts as a factor in the model, to account for declining symptom scores over time because of diminishing pollen exposure at the end of the season. However, the results were identical when the analysis was repeated without pollen counts as a factor.

Safety

There were no clinically meaningful differences between treatment groups in the incidence of clinical or laboratory adverse experiences. Discontinuations because of adverse experiences were infrequent and comparable between the montelukast and placebo treatment groups and between the loratadine and placebo groups (Fig. 1). There was one discontinuation in the placebo group because of a laboratory adverse experience. The majority of the laboratory adverse experiences in all treatment groups were transient and self-limited.

Discussion

Clinical studies have demonstrated the efficacy of montelukast in seasonal allergic rhinitis (5–7). These studies

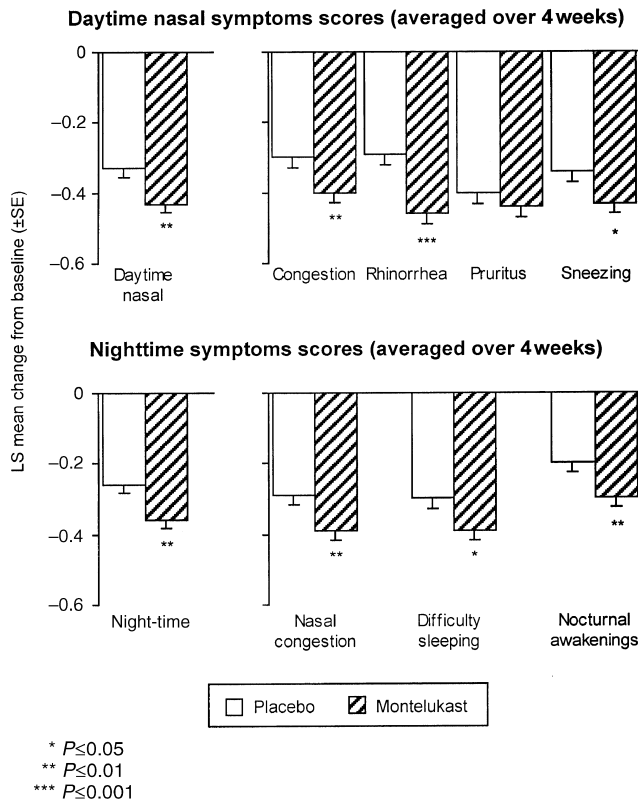


Figure 2. Change from baseline in daytime nasal symptoms scores and night-time symptom scores averaged over 4 weeks of treatment. Symptoms are rated on a scale of 0 (best) to 3 (worst).

utilized an evening dosing schedule, consistent with the approved dosing of montelukast for chronic asthma. Because the pharmacokinetics of montelukast are similar whether it is administered in the morning or the evening (8), efficacy in seasonal allergic rhinitis was anticipated to be independent of the time of dosing. The treatment effect of montelukast relative to placebo over the first 2 weeks of this study for daytime nasal symptoms, night-time symptoms, and composite symptoms scores was similar to the treatment effects reported in previous 2-week studies in which montelukast 10 mg was administered in the evening (6, 7). Thus, montelukast provides comparable treatment effects in both daytime and night-time symptoms of allergic rhinitis independent of the time of dosing. Similar to previous studies, the safety and tolerability of montelukast 10 mg administered over 4 weeks were comparable with placebo, (6, 7) consistent with the experience in patients with asthma (14).

One of the more interesting results of this study was the time course of the treatment effects of montelukast compared with placebo and its apparent difference from that of loratadine when compared with placebo over a 4-week treatment period. When symptoms scores were analyzed by week, the data demonstrated that the treatment effect of montelukast was durable and consis-

tent over the entire 4-week treatment period, with a small increase at week 2 relative to week 1 that was subsequently maintained for the remainder of the treatment period. These results differ from the time course of treatment with loratadine in the daytime nasal symptoms score, in which the magnitude of the loratadine treatment effect diminished with time. A similar trend of decreasing treatment effect of loratadine *vs* placebo was seen for the night-time symptoms score, the daytime eye symptoms score, and the composite symptoms score.

Previous studies in seasonal allergic rhinitis have either averaged symptoms over the entire treatment period or looked at symptoms by week. In order to further analyze the time course of the treatment effect, we employed a slope analysis to examine the effect of time on the treatment effect over the entire study in addition to performing pairwise comparisons by week. The slope analysis provides a method for evaluating the response to treatment throughout the study, thus providing information about treatment effect in the face of the evolving allergic response during the allergy season. Although such an analysis makes the assumption that the time trend of the treatment effect is a linear function, it does provide a good fit to the data and a new way to examine responses to treatment over the entire allergy season. The analysis showed that the treatment effect of montelukast for the primary endpoint (daytime nasal symptoms score) and the secondary endpoints of night-time, daytime eye, and composite symptoms scores increased over time and was greater than the placebo effect. However, the treatment effect of loratadine decreased significantly over time for the primary endpoint and diminished over time for the other three secondary endpoints.

How general are the results of our study? This is the first study of montelukast in allergic rhinitis for a period longer than 2 weeks. There are few studies on the treatment of antihistamines in seasonal allergic rhinitis longer than 4 weeks and even fewer that examined active treatment after symptoms had begun. Grossman et al. (10) evaluated the combination of loratadine and pseudoephedrine *vs* placebo in patients with seasonal allergic rhinitis. The design of that study was similar to our study, except that the primary endpoint was a combination of four nasal symptoms plus eye symptoms. The treatment effect was significant only at the first week of treatment; a graph of the weekly symptom scores showed that the treatment effect size diminished over a 4-week treatment period (10). Ratner et al. (9) examined the effects of ebastine and loratadine over a 4-week treatment period during the fall allergy season. The study design and the daytime nasal symptoms assessed were similar to our study. Although the weekly treatment effect size was not described in the paper by Ratner et al., their graph of the weekly percent change from baseline in daily symptom score is similar to that seen in our study. Notably, a decreasing treatment effect over time was seen for both ebastine and loratadine.

Table 4. Results for loratadine vs placebo

Endpoint	Duration of treatment (weeks)*	LS mean change from baseline† (95% CI)		LS mean difference (95% CI)	P value
		Placebo	Loratadine		
Daytime nasal symptoms score	2	-0.23 (-0.28, -0.18)	-0.45 (-0.52, -0.37)	-0.22 (-0.31, -0.13)	≤ 0.001
	4	-0.33 (-0.38, -0.28)	-0.50 (-0.58, -0.42)	-0.17 (-0.26, -0.08)	≤ 0.001
Night-time symptoms score	2	-0.18 (-0.23, -0.14)	-0.25 (-0.32, -0.19)	-0.07 (-0.15, 0.01)	0.080
	4	-0.26 (-0.31, -0.22)	-0.32 (-0.39, -0.25)	-0.06 (-0.14, 0.02)	0.165
Composite symptoms score‡	2	-0.21 (-0.25, -0.16)	-0.36 (-0.43, -0.30)	-0.16 (-0.23, -0.08)	≤ 0.001
	4	-0.30 (-0.34, -0.26)	-0.42 (-0.49, -0.36)	-0.13 (-0.20, -0.05)	0.002
Daytime eye symptoms score	2	-0.18 (-0.23, -0.14)	-0.33 (-0.41, -0.26)	-0.15 (-0.24, -0.06)	≤ 0.001
	4	-0.27 (-0.32, -0.22)	-0.39 (-0.47, -0.31)	-0.12 (-0.21, -0.03)	0.011
Patient's global evaluation§	2	2.73 (2.59, 2.88)	2.30 (2.08, 2.52)	-0.43 (-0.69, -0.18)	≤ 0.001
Physician's global evaluation§	2	2.75 (2.62, 2.88)	2.38 (2.18, 2.59)	-0.37 (-0.61, -0.13)	0.003
Rhinoconjunctivitis quality-of-life¶	2	-0.55 (-0.65, -0.45)	-0.85 (-1.00, -0.70)	-0.30 (-0.47, -0.13)	≤ 0.001
	4	-0.85 (-0.96, -0.74)	-1.08 (-1.25, -0.91)	-0.23 (-0.43, -0.03)	0.024
Morning (end-of-dosing) nasal symptoms score	2	-0.20 (-0.25, -0.15)	-0.30 (-0.37, -0.22)	-0.10 (-0.18, -0.01)	0.026
	4	-0.28 (-0.33, -0.23)	-0.37 (-0.44, -0.29)	-0.08 (-0.17, 0.00)	0.062
Morning (end-of-dosing) eye symptoms score	2	-0.19 (-0.24, -0.14)	-0.29 (-0.37, -0.22)	-0.10 (-0.19, -0.02)	0.020
	4	-0.28 (-0.33, -0.23)	-0.35 (-0.42, -0.27)	-0.07 (-0.16, 0.02)	0.116
Eosinophil count (×10 ³ cells/μl)	4	0.01 (-0.00, 0.02)	0.01 (-0.00, 0.03)	0.00 (-0.01, 0.02)	0.787

* Mean score during the first 2 weeks or all 4 weeks of treatment.
† Mean score during the 2 or 4-week blinded treatment period minus mean score during 3–5-day placebo run-in period.
‡ Mean of the daytime nasal symptoms score and the night-time symptoms score.
§ Values for global evaluations are absolute scores because this question was asked only at week 2.
¶ Mean of seven Rhinoconjunctivitis quality-of-life domains scored on 0 (best) to 6 (worst) scale.
LS, least squares; CI, confidence interval. *P* value is for the comparison with placebo.
All symptoms were scored on 0 (best) to 3 (worst) scale; rhinoconjunctivitis quality-of-life questions and global evaluations scored on 0 (best) to 6 (worst) scale.

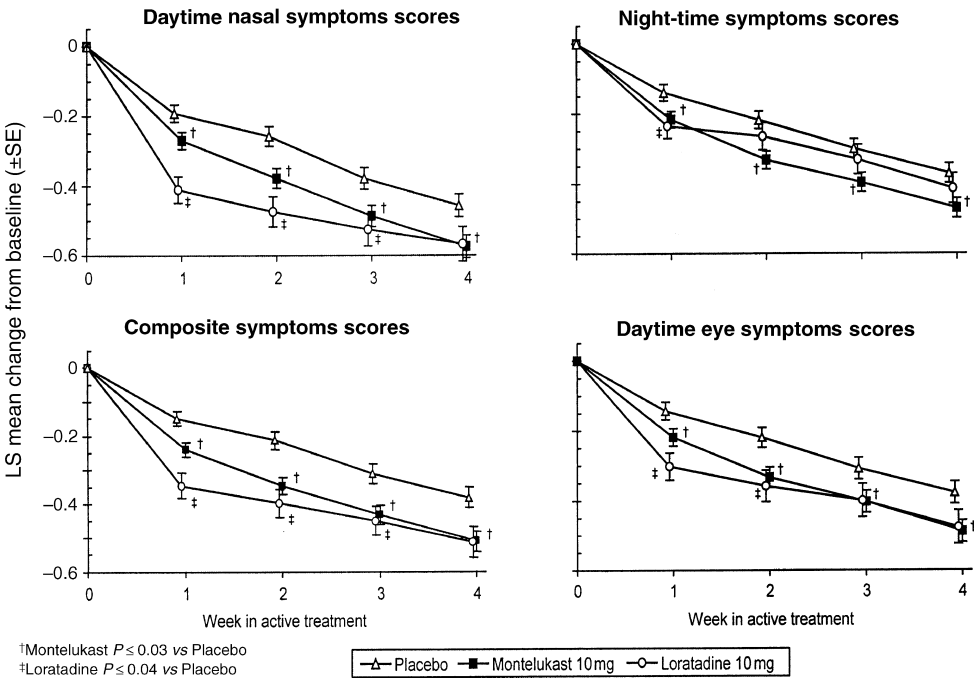


Figure 3. Mean change from baseline by week in key efficacy endpoints.

In contrast to the effects of antihistamines, intranasal administration of corticosteroids has been reported to provide significant improvement in nasal symptoms *vs* placebo in seasonal allergic rhinitis patients during all 4 weeks of double-blind treatment (15–17). These results parallel those that we report here on the durable effect of montelukast throughout the treatment period; this similarity is not surprising because, like montelukast, corticosteroids are anti-inflammatory agents.

Taken together, these previously reported data and the results presented here suggest that over a 4-week treatment period, there may be a diminishing response to antihistamines in seasonal allergic rhinitis. It has been proposed that the decrease in treatment effect over time observed with antihistamines is not a true decrease in efficacy but rather reflects a decrease in symptoms scores because of falling pollen counts at the end of the season. However, this rationale may not be completely correct. First, the treatment effect of montelukast did not diminish during the 4-week treatment period, suggesting that falling pollen counts do not adequately explain diminishing treatment responses. Secondly, the results of the slope analysis were the same whether or not we included pollen counts as a factor, again suggesting that the durability of the montelukast treatment effect and the diminishing loratadine treatment effect (*vs* placebo) were not due to falling pollen counts but rather were intrinsic differences in the responses to these two agents during the pollen season.

What might explain the differing time course of the treatment effects of montelukast and loratadine? One possibility is that the time course of release of leukotrienes differs from that of histamine in allergic rhinitis, thus leading to a dissimilar time course of response to therapy. Surprisingly few studies have examined the time course of mediator release during natural pollen exposure. A study of histamine and LTC₄ levels in nasal washings by week during the allergy season suggested that histamine and LTC₄ release had different kinetics (18). A second possibility is that mediator release is constant, but the nasal mucosa becomes less responsive to histamine during the course of the allergy season. Tachyphylaxis to repeated histamine challenge in the nasal mucosa as well as in the airway of asthmatic patients has been reported (19, 20). However, there is tachyphylaxis to the bronchoconstrictive effects of LTD₄ as well. Tachyphylaxis, therefore, is unlikely to explain these results. The third possibility is that montelukast, but not the antihistamine loratadine, modulates the development of the nasal allergic response during the allergen season. Nasal mucosal exposure to antigen causes local inflammation characterized by infiltration of eosinophils, neutrophils and mononuclear cells (21–23) as well as systemic signs of inflammation such as eosinophilia (24). In this and

previous studies, montelukast reduced blood eosinophil counts (6, 7). Although these data suggest that montelukast could modulate both the systemic and the local allergic response, the effect of montelukast on nasal eosinophilia and markers of the systemic allergic response in allergic rhinitis has yet to be formally investigated.

In summary, montelukast provides significant benefit in the treatment of symptoms of seasonal allergic rhinitis independent of the time of administration. The treatment effect of montelukast is durable, extending over the full 4-week treatment period, and did not diminish with time. The time course of the treatment effect differed from that of the antihistamine loratadine. The reasons for this difference are not yet clear, but the similarity of the time course of response of montelukast to that of nasal steroids suggests that anti-inflammatory actions of montelukast may play a role. The 4-week results presented here, while novel, were obtained from one study. Given that there are few comparable, long-term, placebo-controlled published studies that have similarly examined the effect of antihistamines on the weekly change in symptom scores, more research in this area is clearly needed.

Acknowledgments

This study was supported by a grant from Merck Research Laboratories, Rahway, NJ. The Montelukast Fall Allergic Rhinitis Study Group comprised the following investigators: Atkinson, Dean, MD, Oklahoma City, OK; Banov, Charles, MD, Charleston, SC; Bardelas, Jose, MD, High Point, NC; Berger, William, MD, Mission Viejo, CA; Bowling, Bruce, MD, Endwell, NY; Call, Robert, MD, Richmond, VA; Charlton, Scott, MD, Ozark, AL; Chervinsky, Paul, MD, North Dartmouth, MA; Condemi, John, MD, Rochester, NY; Dykewicz, Mark, MD, St Louis, MO; Feinstein, Barry, MD, Richmond, VA; Finn Jr, Albert, MD, Charleston, SC; Fisher Jr, Chester, MD, Newport News, VA; Given, John, MD, Canton, OH; Goldberg, Pinkus, MD, Indianapolis, IN; Greos, Leon, MD, Englewood, CO; Grogan Jr, Fred, MD, Cordova, TN; Hampel Jr, Frank, New Braunfels, TX; Harris, Pamela, MD, Minneapolis, MN; Jakes, Margaret, MD, Montgomery, AL; Kaiser, Harold, MD, Minneapolis, MN; LaForce, Craig, MD, Raleigh, NC; Lampl, Kathy, MD, Rockville, MD; Larsen, Lawrence, MD, Salt Lake City, UT; Lieberman, Allen, MD, Austin, TX; Lumry, William, MD, Dallas, TX; Maccia, Clement, MD, Warren, NJ; Meltzer, Eli, MD, San Diego, CA; Nayak, Anjali, MD, Normal, IL; Pedinoff, Andrew, MD, Princeton, NJ; Picone, Frank, MD, Tinton Falls, NJ; Pollard, Stephen, MD, Louisville, KY; Ratner, Paul, MD, San Antonio, TX; Richmond, G. Wendell, MD, Oak Brook, IL; Rooklin, Anthony, MD, Upland, PA; Rosenthal, Richard, MD, Fairfax, VA; Rowe, Michael, MD, Novi, MI; Saff, Ronald, MD, Tallahassee, FL; Schenkel, Eric, MD, Easton, PA; Segal, Allen, MD, Dallas, TX; Tripathy, Ita, MD, Rolla, MO; van Bavel, Julius, MD, Austin, TX; Vandewalker, Mark, MD, Columbia, MO; Wald, Jeffrey, MD, Overland Park, KS; Weinstein, Steven, MD, Huntington Beach, CA; Yarbrough, John, MD, Gainesville, GA; Zedler, Barbara, MD, Richmond, VA. We also acknowledge S. Balachandra Dass, PhD, for writing assistance.

References

1. LUNDBACK B. Epidemiology of rhinitis and asthma. *Clin Exp Allergy* 1998;**28** Suppl 2:3–10.
2. MELTZER EO. Role for cysteinyl leukotriene receptor antagonist therapy in asthma and their potential role in allergic rhinitis based on the concept of “one linked airway disease”. *Ann Allergy Asthma Immunol.* 2000;**84**:176–187.
3. 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.
4. American Thoracic Society Workshop. Immunobiology of asthma and rhinitis: pathogenic factors and therapeutic options. *Am Respir Crit Care Med* 1999;**160**:1778–1787.
5. 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**:917–922.
6. NAYAK A, PHILIP G, LU S, MALICE M-P, REISS TF, Montelukast Fall Rhinitis Investigator Group. Efficacy and tolerability of montelukast alone or in combination with loratadine in seasonal allergic rhinitis: a multicenter, randomized, double-blind, placebo-controlled trial performed in the fall. *Ann Allergy Asthma Immunol* 2002;**88**:592–600.
7. PHILIP G, MALMSTROM K, HAMPEL JR FC, WEINSTEIN SF, LAFORCE CF, RATNER PH et al. Montelukast for treating seasonal allergic rhinitis: a randomized, doubleblind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002;**32**:1020–1028.
8. KNORR B, LARSON P, NGUYEN H, HOLLAND S, REISS TF, CHERVINSKY P et al. Montelukast dose selection in 6- to 14-year olds: comparison of single-dose pharmacokinetics in children and adults. *J Clin Pharmacol* 1999;**39**:786–793.
9. RATNER PH, LIM JC, GEORGES GC. Comparison of once-daily ebastine 20 mg, ebastine 10 mg, loratadine 10 mg, and placebo in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 2000;**105**:1101–1107.
10. GROSSMAN J, BRONSKY EA, LANIER BQ, LINZMAYER MI, MOSS BA, SCHENKEL EJ, SELNER JC. Loratadine-pseudoephedrine combination versus placebo in patients with seasonal allergic rhinitis. *Ann Allergy* 1989;**63**:317–321.
11. BAROODY FH, NACLERIO RM. Antiallergenic effects of Hi-receptor antagonists. *Allergy* 2000;**55**:17–27.
12. JUNIPER EF, GUYATT GH. Development and testing of a new measure of health status for clinical trials in rhinoconjunctivitis. *Clin Exp Allergy* 1991;**21**:77–83.
13. JUNIPER EF. Measuring health-related quality of life in rhinitis. *J Allergy Clin Immunol* 1997;**99**:S742–S748.
14. STORMS W, MICHELE TM, KNORR B, NOONAN G, SHAPIRO G, ZHANG J et al. Clinical safety and tolerability of montelukast, a leukotriene receptor antagonist, in controlled clinical trials in patients aged > 6 years. *Clin Exp Allergy* 2001;**31**:77–87.
15. BRONSKY EA, DOCKHORN RJ, MELTZER EO, SHAPIRO G, BOLTANSKY H, LAFORCE C et al. Fluticasone propionate aqueous nasal spray compared with terfenadine tablets in the treatment of seasonal allergic rhinitis. *J Allergy Clin Immunol* 1996;**97**:915–921.
16. LAFORCE CF, DOCKHORN RJ, FINDLAY SR, MELTZER EO, NATHAN RA, STRICKER W et al. Fluticasone propionate: an effective alternative treatment for seasonal allergic rhinitis in adults and adolescents. *J Fam Pract* 1994;**38**:145–152.
17. FINDLAY S, HUBER F, GARCIA J, HUANG L. Efficacy of once-a-day intranasal administration of triamcinolone acetonide in patients with seasonal allergic rhinitis. *Ann Allergy* 1992;**68**:228–232.
18. SKONER DP, LEE L, DOYLE WJ, BOEHM S, FIREMAN P. Nasal physiology and inflammatory mediators during natural pollen exposure. *Ann Allergy* 1990;**65**:206–210.
19. BAROODY FM, WAGENMANN M, NACLERIO RM. Comparison of the secretory response of the nasal mucosa to methacholine and histamine *J Appl Physiol.* 1993;**74**:2661–2671.
20. STRBAN M, MANNING PJ, WATSON RM, O’BYRNE PM. Effect of magnitude of airway responsiveness and therapy with inhaled corticosteroid on histamine tachyphylaxis in asthma. *Chest* 1994;**105**:1434–1438.
21. LINDEN M, SVENSSON C, ANDERSSON M, GREIFF L, ANDERSSON E, DENBURG JA et al. Circulating eosinophil/basophil progenitors and nasal mucosal cytokines in seasonal allergic rhinitis. *Allergy* 1999;**54**:212–219.
22. MIADONNA A, MILAZZO N, GIBELLI S, SALMASO C, LORINI M, TEDESCHI A. Nasal response to a single antigen challenge in patients with allergic rhinitis – inflammatory cell recruitment persists up to 48 hours. *Clin Exp Allergy* 1999;**29**:941–949.
23. WANG D, CLEMENT P, SMITZ J, DE WAELE M, DERDE MP. Correlations between complaints, inflammatory cells and mediator concentrations in nasal secretions after nasal allergen challenge and during natural allergen exposure. *Int Arch Allergy Immunol* 1995;**106**:278–285.
24. WINTHER L, MOSEHOLM L, REIMERT CM, STAHL SKOV P, KAERGAARD POULSEN L. Basophil histamine release, IgE, eosinophil counts, ECP, and EPX are related to the severity of symptoms in seasonal allergic rhinitis. *Allergy* 1999;**54**:436–445.