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Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring

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Summary

Background Cysteinyl leukotrienes are important proinflammatory mediators believed to have a role in allergic rhinitis.

Objective This multicentre, randomized, double-blind, placebo- and active-controlled trial evaluated the effectiveness and tolerability of montelukast, a cysteinyl leukotriene receptor antagonist, for treating patients with seasonal allergic rhinitis.

Methods After a 3- to 5-day, single-blind placebo run-in period, 1302 male and female patients (aged 15–81 years) with active allergic rhinitis symptoms were randomly assigned to receive montelukast 10 mg ($n = 348$), loratadine 10 mg ($n = 602$), or placebo ($n = 352$) administered once daily at bedtime for 2 weeks during the spring allergy season.

Results Mean patient characteristics and symptom scores at baseline were similar for the three treatment groups. The primary end-point, daytime nasal symptoms score (mean of nasal congestion, rhinorrhea, nasal pruritus, and sneezing scores; 0–3 scale), improved from baseline during treatment by (least squares mean, 95% confidence interval) -0.37 (-0.43, -0.31), -0.47 (-0.52, -0.43), and -0.24 (-0.29, -0.18) in the montelukast, loratadine, and placebo groups, respectively ($P \leq 0.001$ comparing each active treatment with placebo). Mean changes from baseline in all other diary-based scores, including night-time and eye symptom scores, were significantly greater for each active treatment than for placebo. The rhinoconjunctivitis quality of life overall score improved significantly with montelukast and with loratadine as compared with placebo. Montelukast and loratadine showed a safety profile comparable to that of placebo.

Conclusion Montelukast is well tolerated and provides improvements in daytime and night-time symptoms, as well as quality of life parameters, for patients with seasonal allergic rhinitis.

Keywords cysteinyl leukotriene type-1 receptor antagonist, H_1-receptor antagonist, loratadine, montelukast, quality of life, rhinoconjunctivitis, seasonal allergic rhinitis

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Introduction

Allergic rhinitis is a common chronic condition, estimated to affect up to 25% of adults and up to 40% of children in developed countries [1–3]. Symptoms of allergic rhinitis result from an IgE-mediated process that is triggered by exposure of the nasal mucosa to airborne allergen. Although the symptoms of allergic rhinitis, which include nasal congestion, rhinorrhea, nasal pruritus, and sneezing, are not life-threatening, they are not trivial for affected patients, who can experience significantly reduced quality of life, cognitive impairment, and sleep disturbances as a result [4–6]. Moreover, the economic burden of allergic rhinitis is substantial, with an estimated $5.9 billion spent in the US in 1996 for direct medical care for allergic rhinitis and related airway conditions [7] and another estimated $2.4 to $4.6 billion associated with at-work productivity losses in 1995 [8]. In Europe, the direct and indirect annual costs of allergic rhinitis were estimated recently to be 1.0–1.5 billion Euro and 1.5–2.0 billion Euro, respectively [2].

The symptoms of allergic rhinitis result from the action of several mediators, the best known of which is histamine, but which also include kinins, tryptase, prostaglandins (particularly PGD_2), and leukotrienes (particularly the cysteinyl leukotrienes LTC_4 and LTD_4) [9]. Several findings support a role for cysteinyl leukotrienes in allergic rhinitis. Firstly, cysteinyl leukotrienes are rapidly synthesized by inflammatory cells considered to play a key role in allergic rhinitis, namely, mast cells, eosinophils, and basophils [9]. Secondly, LTC_4 and LTD_4 are released upon exposure of the nasal mucosa to allergen, with readily measurable increases found in nasal secretions of patients with allergic rhinitis after nasal challenge as well as during natural pollen exposure [9–11]. Finally, nasal challenge with these proinflammatory compounds reproduces

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symptoms of allergic rhinitis, in particular nasal obstruction [12, 13] and rhinorrhea [13]; the response to nasal challenge can be prevented by administration of a leukotriene receptor antagonist [14].

The cysteinyl leukotrienes are important mediators of airway inflammation in asthma as well, as supported by the effectiveness of leukotriene blockade in the treatment of asthma. The cysteinyl leukotriene type-1 ($CysLT_1$) receptor antagonist montelukast is an effective and well-tolerated preventive treatment for asthma in adults and children $\geq$ 2 years of age [15–18], confirming the important role of cysteinyl leukotrienes in this lower airway inflammatory disease. Given the burgeoning understanding of the relationships between asthma and allergic rhinitis, as summarized in recent World Health Organization guidelines entitled 'Allergic Rhinitis and its Impact on Asthma' (ARIA) [19], interest has now turned to understanding the role of cysteinyl leukotrienes in the upper airway inflammatory disease of allergic rhinitis.

The aim of this multicentre, randomized, double-blind, placebo-controlled study was to examine the effectiveness and tolerability of montelukast 10 mg given once daily for 2 weeks for the treatment of patients with seasonal allergic rhinitis. A secondary objective was to evaluate the effectiveness of loratadine, a second-generation non-sedating antihistamine, included in this study as a positive control versus placebo. Our hypothesis was that montelukast 10 mg, administered once daily for 2 weeks, would produce improvement in daytime nasal symptoms, as compared with placebo, for patients with seasonal allergic rhinitis.

Patients and methods

Study design and medications

This was a randomized, double-blind, parallel-group trial performed during spring 2000 at 50 study centres in North America (43 in the US and seven in Canada). There were two study periods: a 3- to 5-day single-blind, placebo run-in period followed by a 2-week double-blind treatment period. The five study visits were each separated by 3–7 days. After pre-study screening (visit 1), patients returned (visit 2) to begin the placebo run-in period, which ended at visit 3, when patients were randomly assigned to double-blind treatment. Visits 4 and 5 occurred after 1 and 2 weeks of double-blind treatment, respectively. Note that this study was originally designed with a fourth treatment arm receiving combination therapy with montelukast and loratadine. Although a previous study showed that the combination of montelukast and loratadine provided significant benefit in seasonal allergic rhinitis compared with loratadine alone [20], a subsequent larger study did not reproduce this finding but did show a significant effect of montelukast monotherapy compared with placebo [21]. After initiation of the current study but before unblinding, the focus of this study was changed to emphasize montelukast monotherapy and, in a protocol amendment, the combination arm was dropped from the study; loratadine was maintained as a positive control arm. Consistent with the amended protocol, data analyses for this study adhered to an amended and prospectively determined data analysis plan. The protocol (with amendments) and informed consents were approved by the institutional review board or ethics review committee for each participating centre. All patients signed a written informed consent agreement before any study procedure was performed.

During the double-blind treatment period, patients were randomly assigned to receive montelukast 10 mg (Singulair®, Merck & Co., Whitehouse Station, NJ, USA), loratadine 10 mg, or placebo, in a double-dummy manner, according to a computer-generated allocation schedule. All medications were taken once daily at bedtime, irrespective of food. Compliance was determined from returned tablet counts.

Patients

Patients were healthy, non-smoking adults aged 15–81 years with a documented clinical history of seasonal allergic rhinitis (for at least 2 years) with exacerbations during the study season (spring). Patients had to exhibit a positive skin-prick test (weal diameter at least 3 mm greater than saline 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 (e.g. a 3-day nasal symptom score sum of at least 18 during the placebo run-in period; see below for further details on symptom scores).

Patients with asthma were not excluded, provided they did not require treatment with drugs other than inhaled short-acting β-agonist bronchodilators (up to eight puffs per day). Study exclusions included perennial rhinitis with little or no seasonal exacerbations; non-allergic rhinitis; substantial, structural nasal obstruction; and upper respiratory tract infection, sinusitis, or ocular infection within 3 weeks before the trial. Pregnant or lactating patients were also excluded.

Medications with anti-allergic activity were required to be withdrawn for an appropriate period before study start and were excluded during the study, including: antihistamines; nasal, ophthalmic, inhaled, oral, and parenteral corticosteroids; cromolyn and nedocromil; oral and long-acting inhaled β-agonists; anticholinergics; theophylline; and other antileukotrienes. Patients could receive immunotherapy, provided it remained at a stable dosage for 6 months before as well as during the trial. No allergic rhinitis or asthma preventive or rescue medications were permitted during the study except inhaled short-acting β-agonists for asthma.

Daily symptom assessment

A symptom diary card (that has been used previously [20]) was to be completed by all patients daily during the placebo run-in period and the blinded treatment period. Daytime symptoms were rated each night before bed (immediately before study drug administration), and night-time symptoms were rated each morning on arising. Daytime nasal symptoms (nasal congestion, rhinorrhea, nasal pruritus, and sneezing) and daytime eye symptoms (tearing, pruritus, redness, and puffiness) were each rated on a 4-point scale as follows: 0, none (symptom not noticeable); 1, mild (symptom noticeable but not bothersome); 2, moderate (symptom noticeable and bothersome some of the time); and 3, severe (symptom bothersome most of the time and/or very bothersome some of the time). Three night-time symptoms were also scored on a 4-point scale and included difficulty going to sleep (0, not at all; 1, little; 2, moderate; 3, very); night-time awakenings (0, not at all; 1, once; 2, more than once; 3,

awake all night); and nasal congestion on awakening (scored as for daytime symptoms).

Rhinoconjunctivitis quality of life

A validated, 28-question rhinoconjunctivitis quality of life questionnaire [22, 23] was administered at the end of the placebo run-in period (baseline value) and at the end of the second week of blinded treatment. This questionnaire evaluated seven quality of life domains: activity, sleep, nasal symptoms, eye symptoms, non-nose and non-eye symptoms, practical problems, and emotions. Patients scored their response to each question on a 7-point scale ranging from 0 (not troubled) to 6 (extremely troubled).

Other measures

At the end of treatment, patients completed a global evaluation of change in their allergic rhinitis. Patients answered the question 'Compared to when I entered the study, my allergic symptoms are . . .' using a 7-point scale ranging from 'Very much better' (0) to 'Unchanged' (3) to 'Very much worse' (6). Physicians answered an analogous single global question regarding the patient's allergic rhinitis, based on a straightforward clinical assessment (history and physical examinations) at study end compared with study entry, without reference to the patient's daily diaries or any other study-based assessment. Peripheral blood eosinophil counts were measured before and after the blinded treatment period. Airborne pollen counts were measured daily for each geographical area in the study using a Rotorod® sampler (Multidata Inc., Minnetonka, MN, USA); pollen counts were determined at a central laboratory and reported as grains/m^3 of air.

Safety

Safety and tolerability were assessed by adverse event reporting and by changes in vital signs, physical examinations, and electrocardiograms between the first visit and the final visit. Laboratory safety parameters (hematology, serum biochemistry, and urinalysis) were assessed before and after the blinded treatment period.

Statistical analysis

The prespecified primary end-point was the daytime nasal symptoms score (mean of the four individual daytime nasal symptom scores). Secondary end-points were the night-time symptoms score (mean of the three individual night-time symptom scores), the daytime eye symptoms score (mean of the four individual eye symptom scores), patient and physician global evaluations, and rhinoconjunctivitis quality of life scores. Other end-points included the daily composite symptoms score (mean of the daytime nasal symptoms score and the night-time symptoms score) and peripheral blood eosinophil counts. Because all end-points other than the daytime nasal symptoms score were considered secondary, no adjustments for multiple comparisons were made to the *P*-values resulting from testing the secondary end-points.

Efficacy analyses included all randomized patients who had a baseline assessment and at least one post-treatment assessment. Mean symptom scores were calculated at baseline (average of daily scores during the placebo run-in period), during treatment (average of daily scores during the double-blind treatment period), and after 1 and 2 weeks of treatment (average of daily scores during weeks 1 and 2, respectively, of the double-blind treatment period). The mean change from baseline during 2 weeks of treatment was computed for the diary-based symptom scores; quality of life questionnaire responses were also computed as mean change from baseline. If one or more than one score was missing, the average change was computed using the remaining scores; no missing values for end-points were imputed. Peripheral blood eosinophil counts were analysed as percent changes from baseline. For all end-points but the peripheral blood eosinophil counts, between-treatment comparisons were performed using an analysis of covariance model with factors for treatment and study centres and using the baseline value of the dependent variable as a covariate. The least squares (LS) means were obtained and 95% confidence intervals (CI) were calculated. An analysis of variance model, with terms for treatment and study centre, was used to analyze global evaluations. Because the percent changes from baseline in peripheral blood eosinophil counts were non-normally distributed, analyses were based on a non-parametric covariance model with factors for treatment and study centres and using the rank of the baseline value as a covariate.

All randomized patients were included in the safety analyses. The incidences of adverse events and laboratory abnormalities were summarized and compared among the treatment groups. Summary statistics were calculated for changes from baseline in vital signs and predefined changes in laboratory tests.

Results

Patients

Of 2404 patients screened, 1302 patients meeting the inclusion criteria were randomly assigned to one of the three treatment groups. At baseline, there were no clinically meaningful differences among the three treatment groups. Overall, about two-thirds of patients were women (65%); most were white (83%) and in the age range of 18–64 years (94%); 88% had a history of allergic conjunctivitis; 27% had a history of asthma; and 9% reported asthma symptoms (not otherwise specified) at some time during the 2 weeks before study entry. Baseline patient characteristics, including demographics, allergic history, and baseline efficacy measures, are provided in Table 1.

A total of 59 patients discontinued treatment after allocation. The rates and reasons for discontinuation were similar among the treatment groups (Table 2). A small number of patients, ranging from eight patients for the symptom score end-points to 23 for the activity domain of the quality of life questionnaire, did not have baseline and/or treatment data and therefore could not be included in the efficacy analyses; however, patient numbers were similar across treatment groups for each given end-point. At the end of treatment, rates of medication compliance in the three groups, as measured by tablet counts, were similar (~99%), as were average exposures to pollen during treatment. Pollen (tree, grass, and weed) counts were recorded daily for the various study centres. Based on the daily pollen counts reported, the average daily exposure to pollen was computed for each patient during their treatment period, then averages were compared among the three treatment groups. The average pollen counts were highly variable, ranging from 1.9 to

Table 1. Patient baseline characteristics

Patient characteristics	Treatment groups		
	Placebo ($n = 352$)	Montelukast ($n = 348$)	Loratadine ($n = 602$)
Demographics			
Age, years	36 ± 12	37 ± 13	36 ± 13
(range)	(15–81)	(15–76)	(15–74)
Sex, *n* (%)			
Male	229 (65)	233 (67)	390 (65)
Female	123 (35)	115 (33)	212 (35)
Race, *n* (%)			
White	290 (82)	288 (83)	504 (84)
Black	18 (5)	21 (6)	36 (6)
Hispanic	24 (7)	13 (4)	25 (4)
Other	20 (6)	26 (8)	37 (6)
Allergic history			
Duration of allergic rhinitis (years)	18 ± 11	18 ± 12	18 ± 12
History of allergic conjunctivitis (% of patients)	90	88	87
History of asthma (% of patients)	29	27	25
Recent asthma symptoms* (% of patients)	11	8	8
Baseline efficacy measures			
Daytime nasal symptoms (score)†	2.10 ± 0.43	2.09 ± 0.44	2.06 ± 0.41
Night-time symptoms (score)†	1.46 ± 0.66	1.43 ± 0.64	1.45 ± 0.64
Daily composite symptoms (score)†,‡	1.83 ± 0.46	1.81 ± 0.45	1.79 ± 0.44
Daytime eye symptoms (score)†	1.44 ± 0.78	1.39 ± 0.77	1.40 ± 0.76
Rhinoconjunctivitis quality of life (overall score)§	3.22 ± 0.99	3.12 ± 0.99	3.09 ± 1.03
Peripheral blood eosinophil counts ($\times 10^3$cells/μl)	0.21 ± 0.13	0.20 ± 0.14	0.20 ± 0.14

Unless otherwise specified, values are mean ± SD. *Presence of asthma symptoms (not further specified) as noted by the patient at some time during the 2 weeks before study start. †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 7 domains scored on 0 (best) to 6 (worst) scale.

Table 2. Discontinued patients, *n* (%)

Reason for discontinuation	Treatment groups		
	Placebo ($n = 352$)	Montelukast ($n = 348$)	Loratadine ($n = 602$)
Lack of efficacy	8 (2.3)	4 (1.1)	8 (1.3)
Clinical adverse experience	1 (0.3)	3 (0.9)	9 (1.5)*
Protocol deviation	2 (0.6)	2 (0.6)	7 (1.2)
Lost to follow-up	1 (0.3)	1 (0.3)	2 (0.3)
Patient withdrew consent	2 (0.6)	1 (0.3)	1 (0.2)
Other	4 (1.1)	1 (0.3)	2 (0.3)
Total patients discontinued	18 (5.1)	12 (3.4)	29 (4.8)

*One of these patients discontinued after randomization because of an adverse experience that started before randomization.

1256.5 pollen grains/m^3/24 h, but were similar among treatment groups. Average pollen counts (mean and range) were 195.7 (6.7–1190), 196.7 (1.9–1094.6), and 211.7 (6.8–1256.5) for placebo, montelukast, and loratadine groups, respectively.

Efficacy

Primary end-point Improvements from baseline in the daytime nasal symptoms score were significantly greater in the montelukast treatment group and the loratadine treatment group compared with the placebo group (Fig. 1a). Mean differences from placebo (in changes from baseline) for the daytime nasal symptoms score and the four individual symptoms that comprise this score (congestion, rhinorrhea, pruritus, and sneezing) are provided in Table 3.

Secondary end-points Patients in both the montelukast and loratadine groups showed significantly greater improvement than those in the placebo group in the night-time symptoms score, the daily composite symptoms score, and daytime eye symptoms score (Fig. 1 and Table 3). When symptoms were assessed by week of treatment, all three treatment groups showed lower symptoms in week 2 (probably related, in part, to decreasing pollen counts), but both active treatment groups showed persistence of treatment effect in week 2 ($P < 0.01$), compared with the placebo group (Fig. 2).

Changes in mean scores from baseline to the end of the second week of treatment for the rhinoconjunctivitis quality of life overall score (mean of the seven domain scores) and for the individual domains are shown in Table 4. Montelukast and loratadine produced significantly greater improvement from baseline than did placebo in the overall quality of life score as well as in each of the individual domain scores, except for the non-nose and non-eye domain (significant for loratadine only).

On the single question that was used to perform a global evaluation of change in allergic rhinitis during the study, montelukast and loratadine each produced significantly greater improvement ($P \leq 0.004$), demonstrated by lower scores, than placebo. The mean patient global evaluation scores were

2.20, 2.13, and 2.62 in the montelukast, loratadine, and placebo groups, respectively; the mean physician global evaluation scores were 2.23, 2.17, and 2.53, respectively.

Additional analyses Peripheral blood eosinophil counts were similar in each group at baseline. After 2 weeks of treatment, there was a significant decrease ($P \leq 0.001$) in the eosinophil numbers in the montelukast group compared with the placebo group, but not in the loratadine group (Fig. 3).

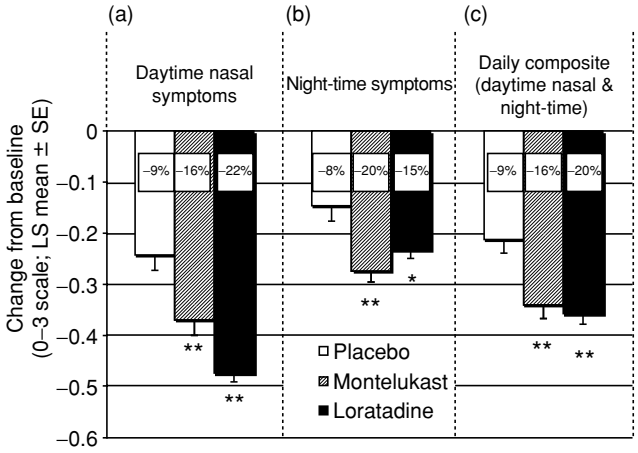

Fig. 1. Mean change from baseline in daily diary-based symptom scores during 2 weeks of blinded treatment. Symptoms are rated on a scale of 0 (best) to 3 (worst). (a) Daytime nasal symptoms score (primary end-point); (b) night-time symptoms score; (c) daily composite symptoms score (mean of the daytime symptoms score and the night-time symptoms score). Data are displayed as LS means ± standard errors; percentages within each bar display the median percent change from baseline for each treatment group. *$P \leq 0.05$ for absolute change compared with placebo. ** $P \leq 0.001$ for absolute change compared with placebo.

Safety No clinically meaningful differences in the incidence of clinical adverse events were apparent among the treatment groups. Overall, 19%, 21%, and 19% of patients in the montelukast, loratadine, and placebo groups, respectively, experienced one or more adverse events. Adverse events occurring in 2% or more of patients in any treatment group were headache (3.2%, 3.5%, and 4.5%, of patients in montelukast, loratadine, and placebo groups, respectively) and upper respiratory infection (1.7%, 1.7%, and 2.3% of patients, respectively). Abnormalities in laboratory test results were infrequent – a total of 11 patients (< 1%) had abnormalities – and similar in frequency among the three treatment groups.

Discussion

We found that montelukast 10 mg administered once daily for 2 weeks during the spring allergy season produced significant improvements, compared with placebo, in the daytime nasal symptoms score among patients with seasonal allergic rhinitis. Montelukast was also significantly more effective than placebo in improving night-time symptoms, daytime eye symptoms, and all quality of life parameters (with the exception of the non-nose and non-eye symptoms domain). Similarly, patient and physician global evaluations at the end of treatment significantly favoured montelukast over placebo. This is the first large clinical trial to demonstrate the benefits of monotherapy with montelukast in seasonal allergic rhinitis. These clinical results of using antileukotriene therapy for seasonal allergic rhinitis complement and validate previous research demonstrating a role for cysteinyl leukotrienes as inflammatory mediators in the pathophysiology of allergic rhinitis [9, 24].

Table 3. Symptoms score end-points: mean differences from placebo in average change from baseline during the treatment period

Symptom score*	Treatment groups			
	Montelukast 10 mg		Loratadine 10 mg	
	LS mean diff. (95% CI)	*P*-value	LS mean diff. (95% CI)	*P*-value
Daytime nasal symptoms	−0.13 (−0.21, −0.06)	≤ 0.001	−0.24 (−0.31, −0.17)	≤ 0.001
Congestion	−0.10 (−0.18, −0.01)		−0.11 (−0.18, −0.03)	
Rhinorrhea	−0.14 (−0.24, −0.05)		−0.24 (−0.32, −0.15)	
Pruritus	−0.12 (−0.21, −0.02)		−0.26 (−0.34, −0.18)	
Sneezing	−0.18 (−0.27, −0.08)		−0.36 (−0.45, −0.28)	
Night-time symptoms	−0.14 (−0.20, −0.07)	≤ 0.001	−0.09 (−0.15, −0.03)	0.003
Difficulty going to sleep	−0.17 (−0.25, −0.09)		−0.11 (−0.18, −0.03)	
Night-time awakenings	−0.14 (−0.21, −0.09)		−0.07 (−0.14, −0.01)	
Congestion on awakening	−0.10 (−0.19, −0.02)		−0.09 (−0.17, −0.02)	
Daily composite symptoms†	−0.13 (−0.20, −0.07)	≤ 0.001	−0.17 (−0.24, −0.11)	≤ 0.001
Daytime eye symptoms	−0.14 (−0.22, −0.06)	≤ 0.001	−0.20 (−0.28, −0.13)	≤ 0.001
Tearing	−0.19 (−0.28, −0.09)		−0.24 (−0.32, −0.15)	
Pruritus	−0.15 (−0.24, −0.05)		−0.27 (−0.35, −0.18)	
Redness	−0.12 (−0.21, −0.03)		−0.16 (−0.24, −0.08)	
Puffiness	−0.13 (−0.22, −0.04)		−0.16 (−0.23, −0.08)	

LS mean diff, least squares mean difference from placebo; CI, confidence interval. *P*-value is for the comparison with placebo. *Mean score during 2-week blinded treatment period minus mean score during 3- to 5-day 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.

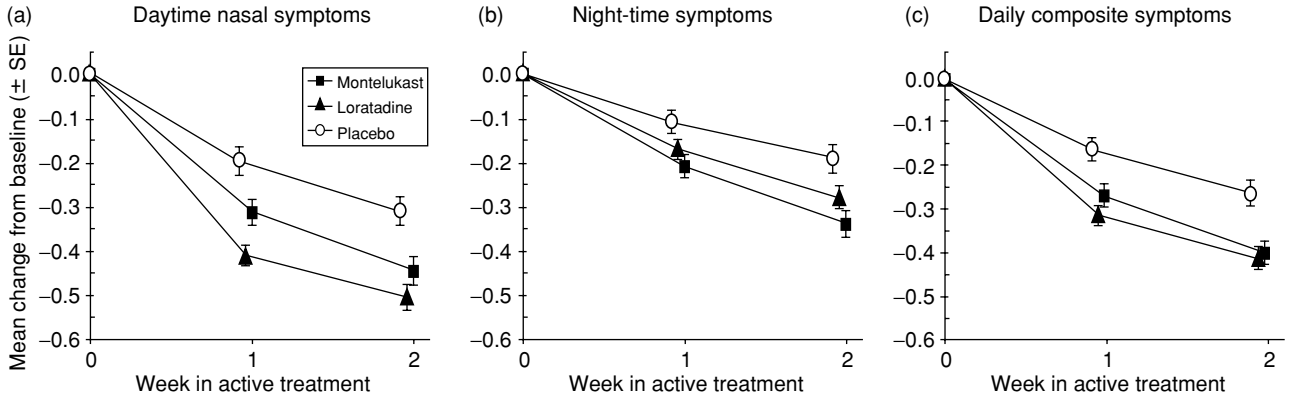

Fig. 2. Mean change from baseline in daily diary-based symptom scores by week of treatment. Symptoms are rated on a scale of 0 (best) to 3 (worst). (a) Daytime nasal symptoms score (primary end-point); (b) night-time symptoms score; (c) daily composite symptoms score (mean of the daytime symptoms score and the night-time symptoms score). Data are displayed as LS means ± standard errors. The baseline values for each score are shown in Table 1.

Table 4. Rhinoconjunctivitis quality of life scores after 2 weeks of treatment with montelukast, loratadine, or placebo

	Change from baseline as LS mean difference (95% CI)		
	Placebo	Montelukast 10 mg	Loratadine 10 mg
Overall score (mean of 7 domains)	−0.65 (−0.76, −0.53)	−0.89 (−1.01, −0.77)	−0.99 (−1.08, −0.90)
P-value versus placebo		0.003	≤ 0.001
Individual domains			
Activity	− 0.87 (−1.03, −0.72)	−1.16 (−1.32, −1.01)	−1.31 (−1.42, −1.19)
P-value versus placebo		0.008	≤ 0.001
Sleep	−0.50 (−0.63, −0.37)	−0.78 (−0.91, −0.65)	−0.74 (−0.84, −0.64)
P-value versus placebo		0.003	0.004
Nasal symptoms	−0.66 (−0.80, −0.52)	−1.00 (−1.14, −0.85)	−1.09 (−1.20, −0.99)
P-value versus placebo		≤ 0.001	≤ 0.001
Eye symptoms	−0.55 (−0.69, −0.41)	−0.79 (−0.93, −0.65)	−0.92 (−1.02, −0.81)
P-value versus placebo		0.012	≤ 0.001
Non-nose & non-eye symptoms	−0.57 (−0.69, −0.45)	−0.67 (−0.79, −0.54)	−0.77 (−0.86, −0.68)
P-value versus placebo		0.277	0.011
Practical problems	−0.72 (−0.86, −0.57)	−1.02 (−1.16, −0.87)	−1.20 (−1.31, −1.09)
P-value versus placebo		0.004	≤ 0.001
Emotions	−0.60 (−0.73, −0.46)	−0.84 (−0.97, −0.70)	−0.89 (−0.99, −0.79)
P-value versus placebo		0.012	≤ 0.001

*Responses to questions are scored on a scale of 0–6, where 0 = best (not troubled) and 6 = worst (extremely troubled).

In other work, zafirlukast, another $CysLT_1$ receptor antagonist, attenuated symptoms of ragweed-induced rhinitis in a 2-day study; in this outdoor natural exposure study, symptoms of nasal congestion, rhinorrhea, and sneezing were each significantly reduced compared with placebo [25]. By contrast, Pullerits and co-workers [26] found no benefit over placebo of twice-daily treatment with zafirlukast 20 mg, whereas intranasal beclomethasone dipropionate alleviated symptoms of rhinitis. A limitation of this study, however, was its small size (11 patients per treatment group). The use of a different approach, concomitant administration of loratadine with montelukast, provided effective treatment for seasonal allergic rhinitis [20]. In that study, montelukast monotherapy produced modest improvements in rhinitis end-points that were similar to those produced by loratadine monotherapy. A different antileukotriene–antihistamine combination has been investigated by Wilson and co-workers [27], who compared the effects of concomitant oral montelukast and cetirizine with those of intranasal mometasone in a placebo-controlled crossover study enrolling 22 patients with seasonal allergic rhinitis. They found that the two active therapy regimens were equally effective and significantly superior to placebo in improving domiciliary peak nasal flow and subjective scores for nasal blockage and total nasal symptoms. In contrast, other studies have shown greater

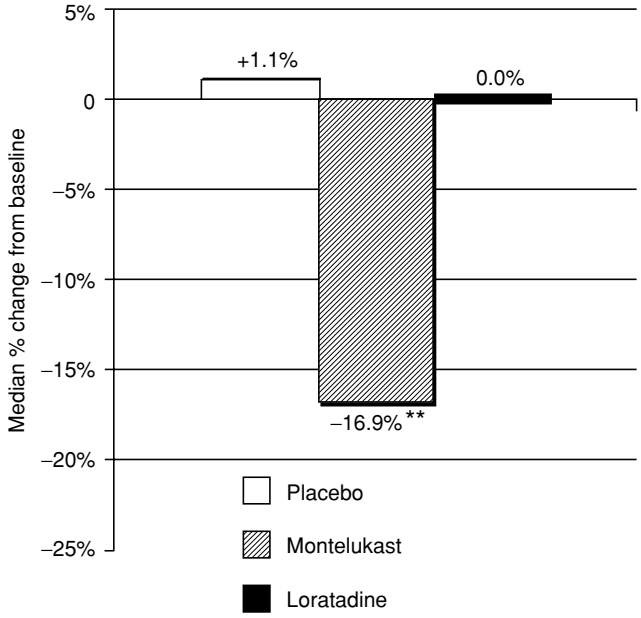

Fig. 3. Median percent change from baseline in peripheral blood eosinophil counts. The baseline values for each treatment group are shown in Table 1. $^{**}P \leq 0.001$ for percent change compared with placebo.

treatment effects of intranasal corticosteroids compared with antihistamine monotherapy [28]. Comparison of intranasal corticosteroids with antileukotriene monotherapy could be addressed in a prospective clinical trial. The effects of montelukast monotherapy in the present study were seen most clearly in night-time symptoms (including difficulty going to sleep and staying asleep, as well as nasal congestion on awakening). Improvement in nasal congestion is not unexpected because nasal challenge with cysteinyl leukotrienes produces nasal blockage [12, 13]. The improvements produced by montelukast in quality of life parameters – including sleep, activity, and emotions domains – are findings that have substantial clinical relevance, as allergic rhinitis is now understood to significantly impair quality of life for affected patients [4, 5].

The finding of a significantly decreased peripheral blood eosinophil count in the montelukast group, compared with placebo, is of interest. Eosinophilia is an important inflammatory aspect of allergic rhinitis; eosinophil influx into nasal mucosa is known to occur in seasonal allergic rhinitis [29]. The reduction in eosinophil count (a 17% median decrease from baseline) after a 2-week treatment period in this study was similar to the progressive decreases in elevated eosinophil counts seen in 12- and 8-week studies of montelukast for adult and pediatric asthma, respectively [16, 17]. The reduction of peripheral blood eosinophils by montelukast suggests that montelukast may have a beneficial effect on allergic inflammation systemically and perhaps even on airway eosinophilia in the nasal mucosa. A reduction in airway eosinophilia by montelukast has been seen in a study of induced sputum in asthma [30], but effects of montelukast on nasal eosinophilia have yet to be formally investigated in rhinitis. Interestingly, montelukast reduced the concentration of leukotrienes in nasal washes of children with asthma [31]; this may reflect an ability of montelukast to reduce influx or activation, or both, of inflammatory cells such as eosinophils that secrete cysteinyl leukotrienes in the nasal mucosa.

Allergic rhinitis is commonly associated with asthma: as many as 38% of patients with allergic rhinitis also have asthma, and as many as 78% of patients with asthma experience nasal symptoms [32]. Also, similar eosinophilic airway inflammation underlies both asthma and allergic rhinitis. The recovery of elevated levels of cysteinyl leukotrienes from the airways of patients with asthma (from bronchoalveolar lavage fluid) and patients with allergic rhinitis (from nasal lavage fluid) support cysteinyl leukotrienes as key elements in the pathophysiology of both diseases [24]. Given the efficacy of montelukast for treating asthma [16–18,33], the finding that montelukast treats allergic rhinitis suggests that it may improve both conditions when they coexist. However, this remains to be established in a prospectively designed clinical trial. In the present study, only 9% of patients reported having recent asthma symptoms (that were not further specified) at some time during the 2 weeks before study start. Of note, patients were excluded from study entry if they required treatment with asthma medications other than inhaled short-acting β-agonists, and neither asthma symptoms nor lung function were evaluated during this study.

To control for the variability of disease seen historically in trials of seasonal allergic rhinitis, we used loratadine as a positive control in this trial. Oral antihistamines, particularly the non-sedating second-generation agents such as loratadine, are well-accepted and widely used therapy for allergic rhinitis [2,34], and thus provide a relevant clinical benchmark. Loratadine therapy produced significantly better results than placebo for all end-points. Symptom reductions with loratadine therapy (in terms of percent change from baseline, relative to placebo change (Fig. 1)) were similar to those seen in previous loratadine studies [35,36], as well as in recent studies of desloratadine, a metabolite of loratadine [37]. A statistical comparison between montelukast and loratadine was not included prospectively in the design of this study, as results from earlier studies [21,38] had suggested that very large patient numbers would be needed for sufficient statistical power to differentiate montelukast from loratadine. On inspection of symptom score data from the present study, mean changes from baseline numerically favoured montelukast over loratadine for the night-time symptoms score (difficulty going to sleep, night-time awakenings, congestion upon awakening); while daytime nasal, eye, and daily composite scores numerically favoured loratadine. Loratadine had no effect on peripheral blood eosinophil counts.

The tolerability profile of montelukast is comparable to that of placebo in short- and long-term clinical trials of patients with asthma [15]. The results of this study concur with the asthma experience. The incidences of adverse events and laboratory abnormalities were similar in the montelukast and placebo groups, as well as in the loratadine group.

In conclusion, the findings of this study support the use of montelukast for treating allergic rhinitis among patients with seasonal symptoms. Montelukast 10 mg once daily is well tolerated and provides significant benefit in seasonal allergic rhinitis, both in reducing daytime and night-time rhinitis symptoms and in improving quality of life outcomes. The efficacy of montelukast in both allergic rhinitis and asthma suggests that montelukast may be of value when the two conditions coexist; this question could be addressed in a study designed prospectively to assess both conditions.

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