Concomitant montelukast and loratadine as treatment for seasonal allergic rhinitis: A randomized, placebo-controlled clinical trial

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Background: Nasal challenge studies have suggested histamine and cysteinyl leukotrienes are important proinflammatory mediators in allergic rhinitis. This study was designed to determine the efficacy of montelukast, a cysteinyl leukotriene receptor antagonist, administered alone or concomitantly with loratadine, an H_1-receptor antagonist, in seasonal allergic rhinitis.
Objective: The purpose of this study was to determine the effect of concomitant use of montelukast and loratadine in the treatment of seasonal allergic rhinitis.
Methods: In this multicenter (N = 12) double-blind, randomized, parallel-group, placebo-controlled 2-week trial, 460 men and women, aged 15 to 75 years, with spring seasonal allergic rhinitis were randomly allocated to receive 1 of the following 5 treatments: montelukast 10 or 20 mg, loratadine 10 mg, montelukast 10 mg with loratadine 10 mg, or placebo, once daily in the evening. The primary end point was daytime nasal symptoms score (average of congestion, rhinorrhea, itching, and sneezing). Other end points were eye symptoms, nighttime symptoms, individual daytime nasal symptoms, global evaluations (patient's and physician's), and rhinoconjunctivitis quality-of-life scores.
Results: Concomitant montelukast with loratadine improved the primary end point significantly ($P < .001$) compared with placebo and each agent alone. Compared with placebo, montelukast with loratadine also significantly improved eye symptoms, nighttime symptoms, individual daytime nasal symptoms, global evaluations, and quality of life. Montelukast alone and loratadine alone caused modest improvements in rhinitis end points. All treatments were similarly well tolerated.
Conclusions: Concomitant montelukast with loratadine provided effective treatment for seasonal allergic rhinitis and associated eye symptoms with a safety profile comparable with placebo. (J Allergy Clin Immunol 2000;105:917-22.)

Key words: *Montelukast, loratadine, cysteinyl leukotriene receptor antagonist, H_1-receptor antagonist, seasonal allergic rhinitis*

Abbreviations used

ANOVA:	Analysis of variance
CI:	Confidence intervals
LS:	Least square
RQLQ:	Rhinoconjunctivitis Quality-of-Life Questionnaire

Allergic rhinitis, the most common allergic disease, is estimated to affect approximately 15% to 20% of the US population. According to some reports, the incidence of allergic rhinitis may be rising.[1] Allergic rhinitis presents with nasal symptoms (congestion, rhinorrhea, itching, and sneezing) and has frequently associated eye signs and symptoms (redness, puffy lids, tearing, and itching) and mouth and throat symptoms (itching of the palate and pharynx and postnasal drainage). In many instances patients also experience headache and fatigue and note significant effect on their quality of life.[2,3] Current treatment guidelines include recommendations for environmental modifications, antihistamines, decongestants, intranasal cromolyn, intranasal anticholinergics, intra-nasal corticosteroids, immunotherapy, and, in intractable cases, systemic corticosteroids.[4,5]

Nasal allergen challenges in immunologically sensitized patients cause the release of inflammatory mediators including histamine and cysteinyl leukotrienes.[6,7] Histamine has long been implicated as a major mediator of allergic rhinitis, causing sneezing, nasal itching, and rhinorrhea. Recent evidence suggests that cysteinyl leukotrienes may also be important mediators, as nasal challenges with them cause congestion and rhinorrhea.[8] In addition, nasal allergen challenge–induced release of cysteinyl leukotrienes has been correlated with rhinitic symptoms.[6,9-14]

The objective of this trial was to determine, in patients with seasonal allergic rhinitis, the efficacy and safety of montelukast, a potent cysteinyl leukotriene-receptor antagonist[15] recently approved for the treatment of chronic asthma,[16] administered alone or concomitantly with loratadine, a nonsedating H_1-receptor antagonist.

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METHODS

Study design

This multicenter (N = 12), randomized, placebo-controlled, parallel-group (5 treatment groups) trial with a 1-week, single-blind, placebo run-in period and a 2-week, double-blind treatment period was conducted between March and May of 1997 in California (San Diego, Orange County, Sacramento, and San Jose–Sunnyvale). The study design included 5 visits, separated by 5 to 10 days. Visit 1 was the prestudy visit and the placebo run-in period started at visit 2. Patients were randomly allocated at visit 3 according to a computer-generated allocation schedule (blocking factor of 10) to receive montelukast (Singulair, Merck) 10 mg, montelukast 20 mg, loratadine (Claritin, Schering-Plough) 10 mg, montelukast 10 mg with loratadine 10 mg, or placebo.

The study medication consisted of 2 bottles containing montelukast 10 mg or matching placebo tablets and 1 containing loratadine 10 mg tablets packaged into capsules or matching placebo capsules; the medication was administered once daily at bedtime, irrespective of food. All labels were collected at trial completion to ensure that blinding had been maintained throughout the study.

The protocol and informed consents for each participating center were approved by an institutional review board. All patients signed a written informed consent agreement.

Patients

Healthy men and women (aged 15 to 75 years) with a clinical history of seasonal allergic rhinitis for at least 2 years and a positive skin test to at least 1 of 8 allergens (Bermuda, Johnson and rye [grass pollens], or olive, oak, elm, sycamore, and walnut [tree pollens]) were eligible for the study. Women were required to have a negative pregnancy test at visit 1 and to agree to use appropriate contraception during the trial. Study exclusions included unstable asthma (emergency department treatment or hospitalization for asthma 1 or 3 months, respectively, before visit 1), use of agents other than short-acting inhaled β-agonists to treat asthma, and electrocardiographic abnormalities including conduction delay and an abnormal QTc interval. Nasal surgery (within 1 year) and an episode of upper respiratory tract infection (rhinitis or sinusitis within 3 weeks) before visit 1 were other exclusions.

Excluded medications were astemizole within 3 months; oral or parenteral corticosteroids within 1 month; cromolyn, nedocromil, or nasal or ophthalmic corticosteroids within 2 weeks; cetirizine, zileuton, zafirlukast, oral or long-acting inhaled β-adrenergic agonists or inhaled anticholinergic agents within 1 week; terfenadine, loratadine, or fexofenadine within 72 hours; and short-acting antihistamines and decongestants within 24 hours before visit 1. Immunotherapy requirements included that if used it needed to have been initiated at least 6 months before visit 1 and be maintained at stable doses during the study.

Daily rhinitis diary card

Recorded on the daily diary card, the allergic rhinitis and conjunctivitis symptoms were assessed on a 4-point scale (0 to 3) for both daytime (completed in the evening) and nighttime (completed on awakening). The daytime questions pertained to nasal (stuffy, runny, itchy nose, and sneezing) and eye (teary, itchy, red, and puffy) symptoms: 0 (not noticeable); 1 (mild symptoms, noticeable but not bothersome); 2 (moderate symptoms, noticeable and disturbing some of the time); 3 (severe symptoms, very disturbing some of the time and/or disturbing most of the time). The nighttime questions pertained to the severity of nasal congestion on awakening, difficulty going to sleep, and nighttime awakenings because of nasal symptoms, and they also used 4-point scales. Similar 4-point scales have shown responsiveness in previous allergic rhinitis trials.[17] Patients had to demonstrate a prespecified level of total daytime nasal symptoms (at least 42 of maximum 84 score) and daytime nasal congestion (at least 13 of maximum 21 score) during the 7-day placebo run-in period to be eligible for randomization.

Other questionnaires

At the randomization visit, before starting study medication, and at the last visit, patients completed the validated Rhinoconjunctivitis Quality-of-Life Questionnaire (RQLQ).[3] The RQLQ evaluates 7 domains: sleep, nonnose and noneye symptoms, practical problems, nasal symptoms, eye symptoms, activities, and emotions using a 0 (best) to 6 (worse) scale. At the last visit (visit 5), patient and physician completed global evaluations by responding to the question "Compared to when I (the patient) entered the study, my (the patient's) overall nose and nonnose symptoms are now" using a 7-point scale (0, very much better; 6, very much worse). Similar global evaluations have been used in recent asthma trials.[16]

Safety

Safety was assessed by adverse experience reporting, physical examinations, electrocardiograms, and laboratory tests (hematology, serum biochemistry, and urinalysis).

Pollen counts

Pollen counts were determined by a central laboratory, Multidata Inc, Minnetonka, Minn, and were reported as pollen grains per cubic meter of air per 24 hours. Rotorod samplers were used to collect pollen in the 4 geographic regions (San Diego, Orange County, Sacramento, and San Jose-Sunnyvale) for 5 sampling periods per week (four 24-hour and one 72-hour period).

Statistical methods

The primary end point was the daytime nasal symptoms score (mean of congestion, rhinorrhea, itching, and sneezing scores recorded as stuffy, runny, itchy nose and sneezing on the diary card). Other end points were the individual nasal symptom scores; global evaluations (patient's and physician's); rhinoconjunctivitis quality of life; nighttime symptoms score (mean score of the 3 nighttime questions); eye symptoms score (mean of tearing, itchy, red, puffy eye scores); and a post hoc composite score capturing the treatment effect over 24 hours (mean of daytime nasal symptoms and nighttime symptoms scores).

The analysis included all patients with at least 1 baseline measurement and 1 measurement during the treatment period. Baseline values were the average values during the run-in period. Efficacy end points (except global evaluations) were analyzed as the average change from baseline over the 2-week treatment period (missing values were not imputed), by use of an analysis of variance (ANOVA) model, with factors for treatment and study center. A two-by-two factorial ANOVA was used to evaluate any interaction between montelukast 10 mg and loratadine 10 mg. The analysis of daytime eye symptoms was prespecified only for patients reporting a history of allergic conjunctivitis.

In addition to the ANOVA, the global evaluations were also analyzed by use of the Cochran-Mantel-Haenszel test based on collapsed categories to determine the percentage of patients whose conditions were better (scores 0, 1, 2), unchanged (score 3), and worse (scores 4, 5, 6) at the end of the study.

All randomized patients were included in the safety analysis. The Fisher exact test was used to determine between-group differences in frequency of clinical and laboratory adverse experiences.

All statistical tests were 2-tailed. Unless otherwise indicated, treatment group averages are reported as mean ± SE in Figure 1 or as least squares (LS) mean with 95% confidence intervals (CI) in

TABLE I. Patient baseline characteristics (mean ± SD)

	Treatment groups				
	Placebo	MNT 10 mg	MNT 20 mg	LRT 10 mg	MNT 10 mg + LRT 10 mg
No. patients	91	95	90	92	90
No. men (%)	45 (49.5)	40 (42.1)	33 (36.7)	43 (46.7)	44 (48.9)
Median age, y (range)	33 (15-75)	33 (15-71)	34.5 (16-68)	34.5 (15-66)	37 (15-74)
History of allergic rhinitis (y)	18 ± 13	18 ± 13	18 ± 12	19 ± 13	17 ± 12
History of allergic conjunctivitis (% patients)	96.7	93.7	95.6	94.6	86.7
Use of immunotherapy (% patients)	5.5	7.4	10.0	12.0	10.0
History of asthma (% patients)	20.9	26.3	32.2	35.9	26.7
Daytime nasal symptoms (score)*	2.07 ± 0.40	2.12 ± 0.38	2.02 ± 0.39	2.07 ± 0.41	2.13 ± 0.42
Daytime eye symptoms (score)*	1.37 ± 0.76	1.47 ± 0.68	1.31 ± 0.69	1.41 ± 0.76	1.47 ± 0.72
Nighttime symptoms(score)*	1.41 ± 0.59	1.51 ± 0.63	1.42 ± 0.61	1.50 ± 0.59	1.45 ± 0.63
Composite score (score)*†	1.78 ± 0.42	1.86 ± 0.43	1.77 ± 0.40	1.82 ± 0.41	1.83 ± 0.44
Rhinoconjunctivitis quality of life (score)‡	3.15 ± 1.05	3.33 ± 0.98	3.06 ± 0.88	3.11 ± 1.02	3.10 ± 1.08

MNT, Montelukast; *LRT,* loratadine.
*0 (best) to 3 (worst) scale.
†Daytime nasal symptoms and nighttime symptoms.
‡0 (best) to 6 (worst) scale.

TABLE II. Discontinued patients

	Treatment groups				
Reason for discontinuation	Placebo (n = 91)	MNT 10 mg (n = 95)	MNT 20 mg (n = 90)	LRT 10 mg (n = 92)	MNT 10 mg + LRT 10 mg (n = 90)
Clinical adverse events	3 (3.3)	0	2 (2.2)	2 (2.2)	1 (1.1)
Lost to follow-up	1 (1.1)	1 (1.1)	1 (1.1)	1 (1.1)	0
Protocol deviations	0	4 (4.2)	1 (1.1)	0	1 (1.1)
Lack of efficacy	1 (1.1)	0	2 (2.2)	2 (2.2)	0
Patient withdrew consent	1 (1.1)	0	0	0	2 (2.2)
Total patients	6 (6.6)	5 (5.3)	6 (6.6)	5 (5.4)	4 (4.4)

MNT, Montelukast; *LRT,* loratadine.

Table III. To adjust for multiple between-treatment comparisons in the primary end point, the Bonferroni procedure was used for the 10 pairwise between-treatment comparisons. The Bonferroni-adjusted *P* values, used for the primary end point, were 10 times larger than the unadjusted *P* values. No formal hypothesis testing was performed for the secondary end points.

Power and sample size

With a sample size of 80 patients per group, the trial had 80% power to detect ($\alpha = 0.05$; 2-sided test) a pairwise between-treatment difference of 0.25 in score change from baseline in the mean daytime nasal symptoms score. The between-treatment difference of 0.25 was estimated from other allergic rhinitis trials using similar 4-point scales (0 to 3).

RESULTS

Patients

Of 834 screened patients, 460 patients were randomly allocated to 1 of 5 treatment groups. Absence of reactivity to 1 or more allergens was the most common reason for excluding patients from randomization. Patient baseline characteristics (Table I) were similar across treatment groups. Twenty-six patients discontinued the study (Table II). Efficacy data were not available from 7 patients; 5 patients (2 placebo, and one each in the montelukast 10-mg, montelukast 20-mg, and loratadine 10-mg groups) failed to return diary cards, and 2 patients (one each in the montelukast 20-mg and loratadine 10-mg groups) had no verifiable data because source documentation was misplaced at the study site.

Efficacy

Concomitant treatment with montelukast and loratadine. Concomitant montelukast and loratadine significantly (Bonferroni-adjusted $P < .001$) improved the primary end point (daytime nasal symptoms score) compared with placebo (Table III) and each agent alone. All other end points, including individual daytime nasal symptom (congestion, rhinorrhea, itching, and sneezing), daytime eye symptoms, nighttime symptoms, and the composite score were significantly improved for montelukast with loratadine compared with placebo (Fig 1 and Table III).

Concomitant montelukast with loratadine, compared with placebo, demonstrated greater improvement in rhinoconjunctivitis quality of life (overall score) (Fig 2) and in patient's and physician's global evaluations. Patients' global scores (mean scores ± SE) were 1.94 ± 0.16 (montelukast with loratadine) and 2.90 ± 0.18 (placebo); $P < .001$. The percentage of patients feeling better, unchanged, and worse is in Fig 3. Physicians' global scores were 2.11 ± 0.15 (montelukast with loratadine) and 2.58 ± 0.16 (placebo); $P < .05$.

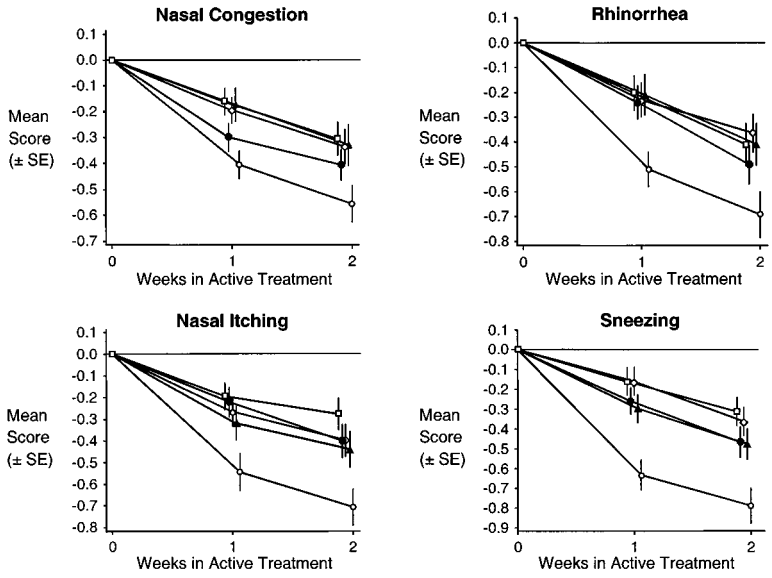

FIG 1. Effect on individual daytime nasal symptoms: nasal congestion, rhinorrhea, nasal itching, and sneezing for each treatment group. The data were collected on daily diary cards using a 0 (= best) to 3 (= worst) scale. Baseline values (score ± SD) were nasal congestion (stuffy nose): 2.38 ± 0.44; rhinorrhea (runny nose): 2.41 ± 0.44; nasal itching (itchy nose): 2.07 ± 0.60; sneezing (sneezing); 1.97 ± 0.67; The data are presented as score, mean change from baseline (± SE). □, Placebo; ●, montelukast 10 mg; ◇, montelukast 20 mg; ▲, loratadine; ○, montelukast 10 mg with loratadine 10 mg. Montelukast with loratadine improved each individual nasal symptom compared with all other treatment groups ($P < .05$), except for nasal congestion score, which was not significantly different from that for montelukast 10 mg.

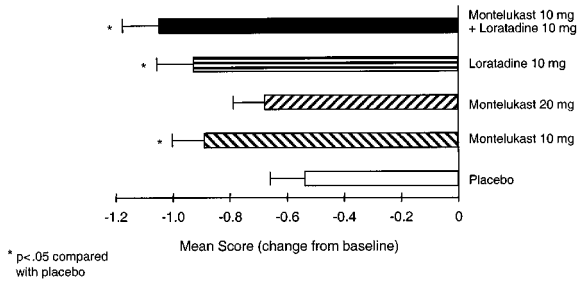

FIG 2. Effect of treatment on the rhinoconjunctivitis quality of life on the pooled seven domains. A 7-point scale (0 = best; 6 = worst) was used. Upper limits of 95% CI are shown.

Montelukast and loratadine treatment. Monotherapy with either montelukast 10 mg (or 20 mg) or loratadine 10 mg was not significantly different from placebo in the primary end point (Table III); however, many of the secondary end points showed significant differences (Figs 1, 2, and 3). Montelukast 20 mg did not provide greater improvement than montelukast 10 mg (Figs 1, 2, and 3; Table III).

Onset of action. Within the first day, montelukast and loratadine given concomitantly significantly ($P < .05$, compared with placebo, montelukast 20 mg, and loratadine 10 mg) improved the primary end point (daytime nasal symptoms score; recorded approximately 24 hours after the first dose) (Fig 4), and nighttime symptoms (recorded approximately 12 hours after the first dose) (data not shown; $P < .05$, compared with placebo). The improvement in daytime nasal symptoms continued over the first 3 days of treatment (Fig 4).

Pollen counts. Pollen counts (tree and grass) were comparable across the 4 regions, ranging from 55 to 90 pollen grains per cubic meter of air per 24 hours. The treatment effect did not appear to vary with the pollen counts.

Safety. The clinical adverse experiences among the treatment groups were similar in frequency and types. The most common clinical adverse experiences were headache (6.6%, 5.3%, 7.8%, 8.7%, and 1.1%) and upper respiratory tract infection (4.4%, 2.1%, 2.2%, 1.1%, and 0%) in the placebo, montelukast 10 mg, montelukast 20 mg, loratadine 10 mg, and montelukast with loratadine groups, respectively.

Laboratory adverse experiences were infrequent and of similar frequency among treatment groups. The number of patients with postrandomization alanine aminotransaminase and aspartate aminotransaminase values above the upper limit of normal were similar among the treatment groups.

DISCUSSION

This is the first clinical trial to demonstrate that a cysteinyl leukotriene receptor antagonist and an H_1-receptor antagonist taken concomitantly provide at least additive efficacy in the treatment of seasonal allergic rhinitis and associated allergic eye symptoms. The trial evaluated the effects of montelukast, a cysteinyl leukotriene receptor

antagonist; loratadine, an H_1-receptor antagonist; and the 2 agents taken concomitantly in patients with seasonal allergic rhinitis. Montelukast 10 mg with loratadine 10 mg provided a large, significant treatment effect compared with placebo and each agent alone in the treatment of allergic rhinitis.

It has been shown that the levels of histamine and cysteinyl leukotrienes are elevated in the nasal secretions of patients with allergic rhinitis when triggered by IgE-mediated reactions.[6] It has also been shown that the release of histamine and leukotrienes contributes to the allergic nasal symptoms by exerting selective effects in the nose. Histamine challenge induces neurologic responses, such as itching and sneezing, by stimulating irritant receptors. However, histamine challenges do not fully reproduce all signs and symptoms of allergic rhinitis, suggesting that other mediators are involved. Other possible mediators are cysteinyl leukotrienes, which are known to influence the glands and vasculature.[12] Both histamine and leukotriene-receptor antagonists have antiallergic and anti-inflammatory properties, including effects on mediator release and chemoattraction of inflammatory cells.[13] These findings suggested that administering histamine and leukotriene modifiers together may result in an amplified effect in the treatment of allergic rhinitis.

Antihistamines, especially the second generation H_1-receptor antagonists (nonsedating and low-sedating antihistamines), are extensively used as treatment of allergic rhinitis,[18] while the clinical experience of treatment in allergic rhinitis with leukotriene modifiers is limited. Two studies have shown that leukotriene modifiers have modest effects on allergic rhinitis: a "day-in-the-park" study with zafirlukast[19] and a nasal-challenge study with zileuton.[20] Similar modest effects were observed in this trial when montelukast was taken alone. Montelukast 10 mg provided the maximal effect; montelukast 20 mg did not provide any improvement over 10 mg. On some end points it appeared that montelukast 20 mg was less effective than 10 mg; however, these differences are most likely because of the measurement variability.

Montelukast alone has demonstrated clinical benefit in asthma.[16] Recently it was shown that montelukast and loratadine taken concomitantly provided greater improvement in chronic asthma than montelukast alone.[21] Zafirlukast, another cysteinyl leukotriene receptor antagonist, and loratadine given twice daily reduced allergen-induced early- and late-phase bronchoconstriction to a larger extent than each therapy alone.[22] These data and the data in this study support the hypothesis that histamine and cysteinyl leukotrienes are important mediators, in both the upper and the lower respiratory airways. Therefore it appears that by blocking the H_1-and the leukotriene receptors simultaneously, enhanced treatment effects can be achieved in both asthma and allergic rhinitis. The end points measured in this study were not sufficiently sensitive to determine whether the effects of montelukast and loratadine were additive or synergistic.

The response to therapy remained constant throughout the 2-week trial. In general, the pollen counts were moderate and without large fluctuations across the 4 regions during the trial. A correlation between the variation in pollen counts and the response to therapy could not be identified.

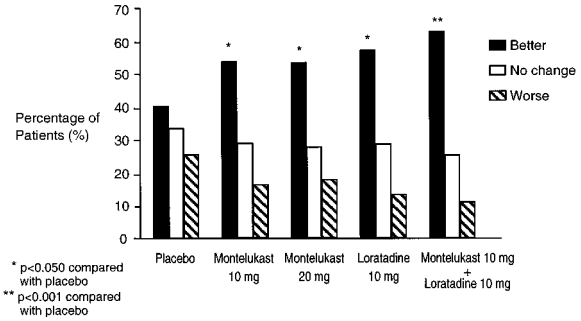

FIG 3. Patients' global evaluations of overall allergic rhinitis symptoms. A 0 (very much better) to 6 (very much worse) scale was used. Data are presented as percentage of patients rating themselves as better (scores = 0, 1, 2), no change (score = 3), or worse (scores = 4, 5, 6).

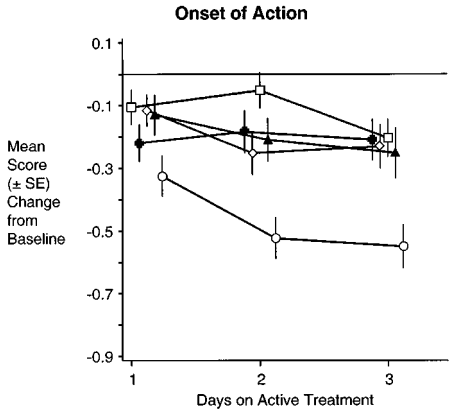

FIG 4. Onset of action. Treatment effects on daytime nasal symptoms during the first 3 days of the treatment period. Data are presented as scores, mean change from baseline (± SE). □, Placebo ; ●, montelukast 10 mg; ◇, montelukast 20 mg; ▲, loratadine; ○, montelukast 10 mg with loratadine 10 mg. Montelukast with loratadine was significantly ($P < .05$) different from placebo, montelukast 20 mg, and loratadine 10 mg on the first day of treatment.

Montelukast[16] and loratadine[23] have been well tolerated in clinical use. In this trial, the frequency of adverse experiences for the individual agents was similar to placebo and no new additional adverse experiences occurred when montelukast and loratadine were taken concomitantly compared with each therapy alone.

In summary, montelukast 10 mg and loratadine 10 mg taken concomitantly once daily were well tolerated and more effective in relieving symptoms of seasonal allergic rhinitis than placebo or each therapy alone. Associated allergy eye symptoms were also reduced. Because asthma and allergic conjunctivitis are frequent comorbidities of allergic rhinitis, concomitant montelukast and loratadine may provide simultaneous and additive clinical benefit for patients who suffer from these prevalent respiratory diseases.

TABLE III. Symptoms score end points: average change from baseline during the treatment period

End point	Placebo*	MNT 10 mg*	MNT 20 mg*	LRT 10 mg*	MNT + LRT*
Daytime nasal†	-0.25	-0.36	-0.29	-0.34	-0.61‡§
	(-0.36, -0.15)	(-0.47, 0.26)	(-0.39, 0.18)	(-0.44, 0.23)	(-0.72, -0.51)
Daytime eye ‖	-0.08	-0.28¶	-0.14	-0.25	-0.46‡
	(-0.21, 0.05)	(-0.40, -0.15)	(-0.27, 0.02)	(-0.37, 0.12)	(-0.59, -0.33)
Nighttime	-0.11	-0.29¶	-0.21	-0.19	-0.33¶
	(-0.22, -0.01)	(-0.39, -0.19)	(-0.31, 0.10)	(-0.30, 0.09)	(-0.43, -0.22)
Composite (daytime nasal and nighttime)	-0.24	-0.39¶	-0.31	-0.32	-0.54‡
	(-0.34, -0.15)	(-0.48, -0.30)	(-0.41, 0.22)	(-0.41, 0.22)	(-0.64, -0.44)

MNT, Montelukast; *LRT,* loratadine.
*LS mean and 95% confidence intervals for the mean.
†Primary end point.
‡$P < .001$ compared with placebo.
§Bonferroni-adjusted P value for the primary end point: $P < .001$.
‖Analysis limited to patients with a history of allergic conjunctivitis.
¶$P < .05$ compared with placebo.

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