Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis

Piyush Patel, MD, FRCP(C)*; George Philip, MD†; William Yang, MD, FRCP(C)‡; Robert Call, MD§; Friedrich Horak, MD¶; Craig LaForce, MD‖; Leen Gilles, MS†; Graigory C. Garrett, BS†; S. Balachandra Dass, PhD†; Barbara A. Knorr, MD†; and Theodore F. Reiss, MD†

Background: Perennial allergic rhinitis (PAR) is a persistent allergic inflammation of the upper respiratory tract due to year-round allergen exposure.

Objective: To evaluate the leukotriene receptor antagonist montelukast for the treatment of PAR.

Methods: Protocol 265 was a 2-arm study performed during the winter. After a placebo run-in period, adults with perennial allergen sensitivity and active symptoms of PAR were randomized to receive 10 mg of montelukast (n = 1,002) or placebo (n = 990) once daily during a 6-week, double-blind, active-treatment period. The primary end point was the daytime nasal symptoms score, defined as the average of scores for nasal congestion, rhinorrhea, and sneezing rated daily by patients.

Results: Statistically significant improvements in PAR symptoms were seen in patients treated with montelukast. Their daytime nasal symptoms scores were reduced during treatment compared with those of the placebo group: the difference between treatments in least squares mean change from baseline was −0.08 (95% confidence interval [CI], −0.12 to −0.04; $P < .001$). Montelukast treatment also improved global evaluations of allergic rhinitis by patients and Rhinoconjunctivitis Quality of Life Questionnaire scores: differences vs the placebo group were −0.15 (95% CI, −0.27 to −0.04; $P < .01$) and −0.15 (95% CI, −0.24 to −0.06; $P < .001$), respectively. Other end points that showed statistically significant improvement with montelukast treatment were nighttime symptoms and each of the 4 nasal symptoms (congestion, rhinorrhea, sneezing, and itching). The treatment effects of montelukast were stable and persistent during the entire 6 weeks of treatment.

Conclusion: Montelukast provided statistically significant relief of PAR symptoms during 6 weeks of treatment.

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INTRODUCTION

Allergic rhinitis is an allergen-induced inflammation of the upper respiratory tract. Interaction of the allergen with mast cells and antigen-presenting cells in the mucosal tissue activates and further recruits these and other cells, such as eosinophils and basophils, resulting in the release of cytokines and proinflammatory mediators, including histamine, prostaglandins, and leukotrienes.[1] The resulting symptoms of nasal congestion, rhinorrhea, sneezing, and itching are characteristic of allergic rhinitis.

Allergic rhinitis may be seasonal or perennial, distinguished by the timing of exposure to causative allergens. Thus, unlike seasonal allergic rhinitis (SAR), perennial allergic rhinitis (PAR) is persistent and chronic, resulting from sensitivity and exposure to year-round (generally household) allergens, such as house dust mites, animal dander, molds, and cockroach allergens.[2] The disorder is common: up to 18% of the general population has been reported to have perennial symptoms.[2–4]

Montelukast is a cyteinyl leukotriene receptor antagonist that has shown efficacy in the treatment of the symptoms of SAR.[5] Improvements (vs placebo) were seen in daytime nasal symptoms, nighttime symptoms, daytime eye symptoms, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores, global evaluations of allergic rhinitis by the patient and by the physician, and peripheral blood eosinophil counts.[6–11] Because SAR and PAR are characterized by a common inflammatory pathology associated with the involvement of leukotrienes, we evaluated the efficacy of montelukast treatment in patients with PAR.

METHODS

Study Design

Protocol 265 was a 2-period, randomized, parallel-group, double-dummy study performed between the fall and spring seasons (outside the pollen season) of 2003 to 2004 at 122 medical centers in the United States and Europe. After a single-blind, placebo run-in period of 5 to 7 days, patients were randomized (using a computer-generated schedule) to receive 10 mg of montelukast (n = 1,002) or placebo (n = 990) daily at bedtime during the 6-week, double-blind, ac-

* Allied Research International, Mississauga, Ontario.
† Merck Research Laboratories, Rahway, New Jersey.
‡ University of Ottawa Medical School, Ottawa, Ontario.
§ Richmond Allergy and Asthma Specialists, Richmond, Virginia.
¶ University of Vienna, Vienna, Austria.
‖ North Carolina Clinical Research, Raleigh, North Carolina.
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tive-treatment period. Safety and tolerability were evaluated by recording adverse events throughout the run-in and treatment periods. The safety analysis included all randomized patients who received at least 1 dose of study therapy.

Patients

Patients were 15 to 85 years old and had at least a 2-year clinical history of PAR and at least a mild-to-moderate level of daytime nasal symptoms (defined in the "End Points" subsection) during the placebo run-in period. Eligible patients had to demonstrate a positive skin test reaction (wheal diameter $\geq$3 mm greater than the control) to 2 or more perennial allergens. The antigens tested were extracts of dust mites *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*, cat antigen (pelt), dog antigen (epithelium), a mixed extract of German and American cockroaches, and a mixed extract of perennial fungi (*Penicillium* species and *Aspergillus* species). Asthmatic patients requiring only as-needed inhaled, short-acting β-agonists were allowed to participate in the study. Patients with other respiratory and ocular disorders were not permitted to participate. Additional therapy for asthma, including corticosteroids and long-acting β-agonists, and the use of other confounding medications (including antihistamines and decongestants) were not permitted. The study was approved by the ethical review committees for each study site, and all the patients gave written informed consent before any study procedure was performed.

End Points

Patients completed a daily diary during the run-in and treatment periods and scored each symptom on a 4-point scale (0 = none and 3 = severe symptoms). The primary end point was the daytime nasal symptoms score, which was defined as the average of scores for nasal congestion, rhinorrhea, and sneezing. One secondary end point—the RQLQ score[12]—was rated by patients using a 7-point scale before randomization and at the end of the 6-week treatment period. The other secondary end point was the global evaluation of allergic rhinitis by the patient, which consisted of a single question, using a 7-point scale (0 = very much better and 6 = very much worse), that evaluated the clinical status of allergic rhinitis at the end of treatment relative to study entry.

Several additional end points were measured, including the nighttime symptoms score (average of the scores for nasal congestion on awakening, difficulty going to sleep, and nighttime awakenings), the daily rhinitis symptoms score (average of the daytime nasal symptoms score and the nighttime symptoms score), the end-of-day nasal symptoms score (symptoms as evaluated in the evening, using instantaneous recall, at the end of the once-daily dosing interval), and the daytime nasal symptom of itching. These additional diary-based end points have been reported in previous SAR studies.[7–11]

Statistical Analysis

The primary efficacy analysis was performed using a modified intention-to-treat approach that included all patients with efficacy measurement at baseline and at least 1 time during treatment. The diary-based end points were analyzed as the change from baseline averaged during the entire 6 weeks of treatment. The RQLQ score was analyzed as the change from baseline at the end of the 6-week treatment period. Statistical analysis was performed using an analysis of covariance model, with treatment and study site as factors and the baseline value of the dependent variable as a covariate. The time course of the treatment effect for the daytime nasal symptoms score was also analyzed: the effect across time was evaluated by a repeated-measures analysis using the 6 weekly scores and by a slope analysis of the weekly scores using a mixed-model approach. For categorical analyses of the RQLQ score, the Fisher exact test was used to compare percentages of patients between treatment groups. Global evaluation of allergic rhinitis by the patient was analyzed using an analysis of variance model, with treatment and study site as factors. Treatment differences were expressed for all the end points as least squares means and 95% confidence intervals (CIs). A sample size in each of the 2 treatment groups of 800 patients completing the 6-week treatment period provided 90% power to detect a treatment difference of 0.075 between the 2 groups (SD = 0.46) for the primary end point of daytime nasal symptoms score.

RESULTS

Patients and Baseline Characteristics

Of 3,401 patients screened, 1,992 were randomized and 1,819 (91%) completed the study (Fig 1); the dropout rate of 9% during the 6-week treatment period was lower than anticipated. Baseline patient characteristics, including demographics, allergic history, and scores for efficacy measures, are listed in Table 1. The mean patient age was 36 years, and most patients were women (64.1%). Baseline efficacy measures were similar between the montelukast and placebo treatment groups. There were no clinically meaningful differences between the 2 groups for any baseline characteristic.

Efficacy

Montelukast demonstrated statistically significant efficacy during the 6-week treatment period in improving symptoms of PAR. The primary end point of daytime nasal symptoms score (average of the nasal congestion, rhinorrhea, and sneezing scores) was reduced in the montelukast group compared with the placebo group: the difference between treatments in mean change from baseline was -0.08 (95% CI, -0.12 to -0.04; $P \leq .001$) (Table 2). Each individual symptom of the primary end point (nasal congestion, rhinorrhea and sneezing), and the symptom of daytime nasal itching, showed statistically significant improvement with montelukast therapy during the 6-week double-blind period (Fig 2).

Montelukast showed a significant ($P \leq .05$) and persistent benefit compared with placebo during each of the 6 weeks of the study (Fig 3). The treatment effect was consistent relative to placebo throughout the treatment period: a slope analysis of the weekly daytime nasal symptoms scores showed a slope (change per week) of -0.06 for montelukast, which was

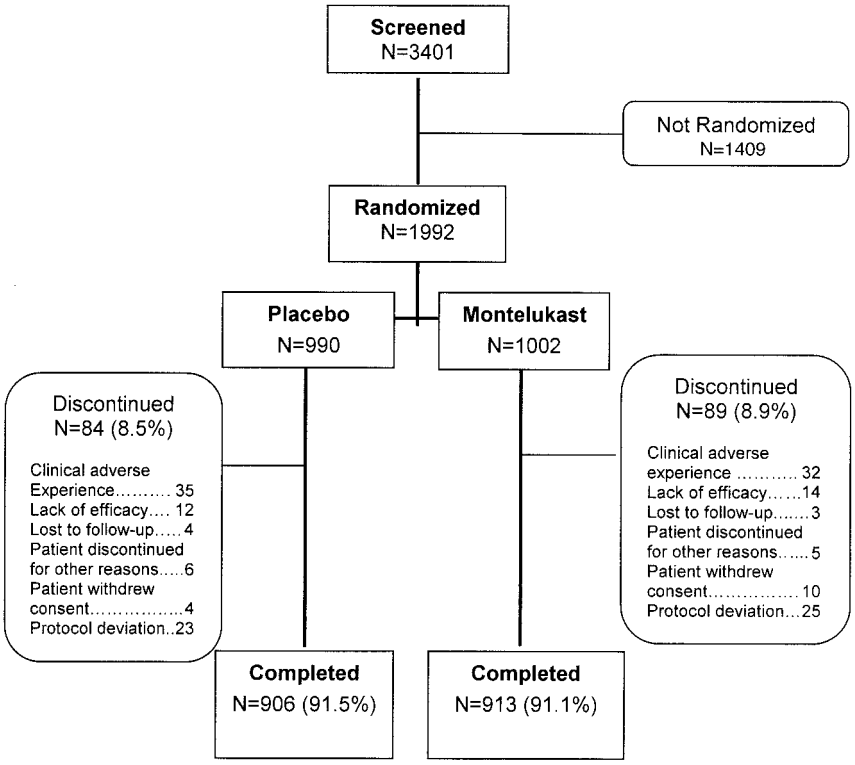

Figure 1. Patient disposition.

Table 1. Baseline Characteristics of the 1,992 Randomized Patients

	Montelukast group (n = 1,002)	Placebo group (n = 990)
Age, mean ± SD (range), y	36.3 ± 13.6 (15–81)	36.6 ± 13.1 (15–79)
Female sex, No. (%)	644 (64.3)	632 (63.8)
Race, No. (%)		
White	839 (83.7)	818 (82.6)
Black	84 (8.4)	78 (7.9)
Hispanic	52 (5.2)	56 (5.7)
Other	27 (2.7)	38 (3.8)
Type of allergic rhinitis, No. (%)		
Perennial (year-round) with seasonal flare-ups	823 (82.1)	805 (81.3)
Perennial (year-round) without seasonal flare-ups	179 (17.9)	185 (18.7)
Additional allergic history, No. (%)		
History of allergic conjunctivitis	831 (82.9)	835 (84.3)
History of asthma symptoms	274 (27.3)	288 (29.1)
Current asthma symptoms	79 (7.9)*	87 (8.8)
Baseline efficacy measures, mean ± SD		
Daytime nasal symptoms score†	2.09 ± 0.40	2.10 ± 0.41
Rhinoconjunctivitis Quality of Life Questionnaire score‡	2.94 ± 1.04	2.96 ± 1.10
Nighttime symptoms score†	1.56 ± 0.60	1.59 ± 0.62
Daily rhinitis symptoms score†	1.83 ± 0.43	1.85 ± 0.45
End-of-day nasal symptoms score†	1.83 ± 0.56	1.85 ± 0.59

* Data are missing for 2 patients.
† Mean score during the placebo run-in period; all symptoms were scored on a scale from 0 (none) to 3 (severe symptoms).
‡ Mean of 7 domains scored on a scale from 0 (best) to 6 (worst).

Table 2. Results for Efficacy End Points During the 6-Week Treatment Period

	Change from baseline, mean ± SD (%)*		Treatment difference, LS mean (95% CI)†
	Montelukast	Placebo	
Primary end point			
Daytime nasal symptoms score	−0.42 ± 0.51 (−19.5)	−0.35 ± 0.48 (−16.0)	−0.08 (−0.12 to −0.04)‡
Secondary end points			
RQLQ score	−0.81 ± 1.14 (−25.1%)	−0.68 ± 1.14 (−19.3)	−0.15 (−0.24 to −0.06)‡
Global evaluation of allergic rhinitis by the patient§	2.28 ± 1.29	2.44 ± 1.29	−0.15 (−0.27 to −0.04)¶
Other end points			
Nighttime symptoms score	−0.30 ± 0.48 (−16.5)	−0.25 ± 0.47 (−13.0)	−0.06 (−0.10 to −0.02)‡
Daily rhinitis symptoms score	−0.36 ± 0.45 (−19.2)	−0.30 ± 0.43 (−15.7)	−0.07 (−0.10 to −0.03)‡
End-of-day nasal symptoms score	−0.35 ± 0.53 (−16.8)	−0.30 ± 0.50 (−13.8)	−0.06 (−0.10 to −0.02)¶

Abbreviations: CI, confidence interval; LS, least squares; RQLQ, Rhinoconjunctivitis Quality of Life Questionnaire.
* Baseline efficacy values for these end points are provided in Table 1.
† Montelukast − placebo.
‡ $P \leq .001$.
§ Global evaluation of allergic rhinitis by the patient is given as mean ± SD treatment score as assessed at the end of the 6-week treatment period relative to study entry on a scale from 0 (best) to 6 (worst).
¶ $P \leq .01$.

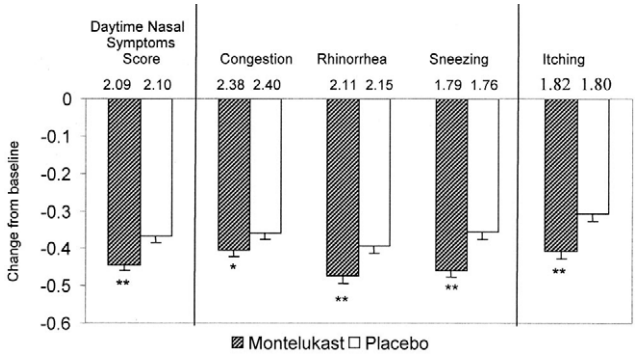

Figure 2. Least squares mean change in the daytime nasal symptoms score; its component nasal symptom scores of congestion, rhinorrhea, and sneezing; and the individual symptom of itching during the 6-week treatment period. Baseline scores are shown above the columns. Asterisk indicates $P <$ .05; repeated asterisk, $P <$ .001. Error bars represent SE.

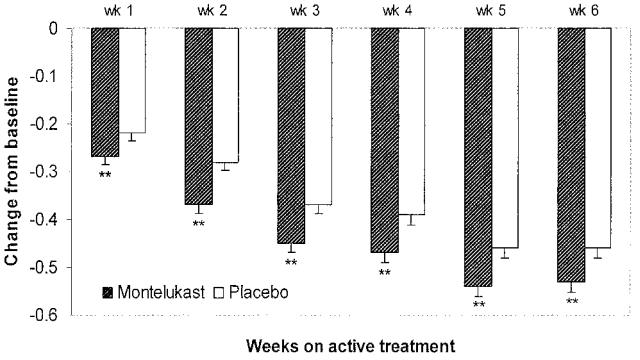

Figure 3. Least squares mean change from baseline in the daytime nasal symptoms score during the 6-week treatment period by week of treatment. Mean baseline scores for the montelukast and placebo groups were 2.09 and 2.10, respectively. Repeated asterisk indicates $P \leq .01$. Error bars represent SE.

similar to the slope of −0.05 for placebo, demonstrating the constant (ie, parallel) effect of montelukast vs placebo throughout the entire 6 weeks of treatment.

Montelukast improved rhinitis-specific quality of life compared with placebo: the difference between treatments in mean change from baseline in the RQLQ score was −0.15 (95% CI, −0.24 to −0.06; $P \leq .001$) (Fig 4). In addition, all 7 domains of the RQLQ (activity, sleep, non-nose/non-eye, practical problems, nasal, eye, and emotions) were statistically significantly improved with montelukast relative to placebo (Fig 4). Additional post hoc analyses examined the proportion of patients who demonstrated a clinically important improvement in their overall RQLQ score. An improvement from the baseline score of at least 0.5 has been identified as a clinically important change in rhinitis-specific quality of life[13]; more patients taking montelukast than placebo showed an improvement in quality of life at this clinically significant level ($P = .02$) (Table 3). Similarly, the post hoc examination of a larger level of change of at least 1.0 showed that more patients taking montelukast than placebo achieved this level of improvement in quality of life ($P = .01$).

Montelukast improved the global evaluation of allergic rhinitis by the patient: the mean difference between treatments was −0.15 (95% CI, −0.27 to −0.04; $P <$ .01) (Table 2). Other end points that showed significant improvement with montelukast (vs placebo) treatment included the nighttime symptoms score ($P \leq .001$), the daily rhinitis symptoms score ($P \leq .001$), and the end-of-day nasal symptoms score ($P = .007$) (Table 2). Similarly, significant mean differences between treatments were seen in 2 of the 3 individual symptoms of the nighttime symptoms score (difficulty going to sleep and nighttime awakening [$P <$ .01]; the third nighttime

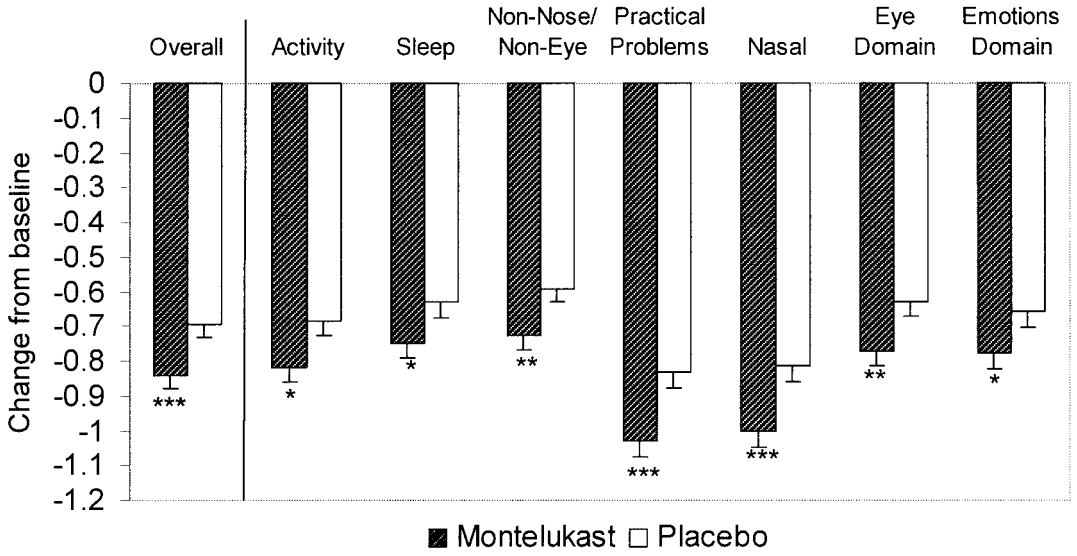

Figure 4. Least squares mean change from baseline in the Rhinoconjunctivitis Quality of Life Questionnaire overall and domain scores at the end of the 6-week treatment period. Asterisk indicates $P \leq .05$; repeated asterisk, $P \leq .01$; triple asterisk, $P \leq .001$. Error bars represent SE.

Table 3. Patients With an Improvement From Baseline in the Rhinoconjunctivitis Quality of Life Questionnaire Score of at Least 0.5 or at Least 1.0

Patient improvement	Patients, No. (%)		*P* value for difference
	Montelukast (n = 977)	Placebo (n = 969)	
≥0.5	570 (58.3)	514 (53.0)	.02
≥1.0	386 (39.5)	328 (33.8)	.01

symptom of nasal congestion on awakening was borderline significant [$P = .052$]).

Safety

There were no clinically meaningful differences between the montelukast and placebo groups in the incidence of clinical adverse experiences. Discontinuations due to adverse experiences were infrequent and were comparable between the montelukast and placebo treatment groups (Fig 1).

DISCUSSION

Perennial allergic rhinitis adds a considerable burden to the health, financial condition, and social lives of patients. Not surprisingly (given the year-round nature of the disease), patients with PAR had significantly higher allergy-related health care costs and greater use of concomitant medications compared with patients with SAR.[3] Furthermore, patients with PAR report a consistently poorer health-related quality of life compared with healthy subjects.[14] Bousquet et al[15] reported that patients with PAR showed a significant impairment in 8 of 9 quality-of-life dimensions; the level of impairment was comparable with that seen in asthmatic patients.

Antileukotriene drugs, such as montelukast, have shown clinical benefit in the treatment of asthma and SAR, 2 allergic diseases characterized by inflammation of the respiratory airways.[5] Few studies have described the treatment of PAR with such agents. Pranlukast was shown to decrease inflammatory cell markers and chemical mediators in the nasal mucosa of patients with PAR.[16] A pilot study[17] of children with exercise-induced asthma and PAR showed improvement in levels of inflammatory markers (interleukin 4, interleukin 13, and interferon-γ) in nasal lavage after treatment with montelukast. In another small study[18] in children with PAR, montelukast significantly improved nasal peak expiratory flow rates, total symptom scores, and quality-of-life measures and decreased blood eosinophil levels.

In the present study, adults treated with montelukast showed a statistically significant improvement in symptoms of PAR, measured primarily as the daytime nasal symptoms score (composed of the nasal congestion, rhinorrhea, and sneezing scores). In particular, montelukast showed statistically significant effectiveness in relieving the individual symptom of nasal congestion. This is important because nasal congestion is the predominant symptom of PAR due to chronic allergic inflammation of the nasal mucosa that results from a mixture of proinflammatory mediators, such as leukotrienes and histamine released from mast cells, eosinophils, or basophils.[2,4] This greater inflammatory burden imposed by PAR makes this disorder more difficult to treat than SAR.

We report that the use of montelukast statistically significantly decreased nasal congestion during a 6-week period. In addition, the individual symptoms of rhinorrhea and sneezing showed statistically significant improvement with montelukast treatment. These results were not unexpected because montelukast has previously been shown to have a beneficial

effect on the 3 nasal symptoms of congestion, rhinorrhea, and sneezing in SAR.[7–11] Nasal itching, which is less prominent in PAR than in SAR, was not a part of the primary end point of this study. Nevertheless, the montelukast group demonstrated a statistically significant improvement in this symptom in this study as in SAR, demonstrating the efficacy of montelukast over a broad spectrum of rhinitis symptoms.

Because PAR is a chronic disorder associated with continual exposure to allergens year-round, medications to treat symptoms should demonstrate a persistent effect across time. Although many studies[4,19–21] on the treatment of PAR with intranasal corticosteroids and antihistamines have been conducted using treatment periods of up to 4 weeks, fewer studies[22–24] of 6 to 12 weeks or longer have been reported. This issue has gained new prominence under the disease classification scheme recently described by the World Health Organization in which patients with symptoms of allergic rhinitis present for more than 4 weeks are classified as having "persistent allergic rhinitis."[4] Our study is thus one of the few placebo-controlled studies examining several clinical efficacy measures in patients with PAR during a timeframe consistent with persistent allergic rhinitis. Furthermore, few studies have explicitly reported whether treatment effects for PAR remain undiminished by week of treatment. In one such study,[22] ebastine significantly improved nasal symptoms averaged across a 12-week period and also at week 1 of treatment but did not differ significantly from placebo during any of the subsequent 11 weeks of treatment. In contrast, our study shows that the efficacy of montelukast remained undiminished after more than 6 weeks of treatment. The effect across time of montelukast paralleled that of placebo, suggesting that this treatment effect may persist beyond the 6-week winter treatment period that was studied, although a longer study is required to confirm the long-term efficacy of montelukast in PAR, as already shown for montelukast in chronic asthma.[25,26]

The presence of nighttime symptoms in allergic rhinitis is sufficient to categorize patients as having moderate-to-severe disease.[4] Nocturnal sleep disturbances can lead to the functional impairment of daytime activities.[27] The nighttime symptom score in this study showed statistically significant improvement with montelukast therapy compared with placebo use. Another diary-based end point that showed statistically significant improvement with montelukast use was the daily rhinitis symptoms score, a composite of the daytime nasal symptoms score and the nighttime symptoms score. This score reflects treatment efficacy across a 24-hour period, and the statistically significant reduction in this score is further evidence of the beneficial effect of once-daily montelukast use throughout the day and night. These results were supported by the end-of-day nasal symptoms score, which evaluated nasal symptoms as felt by patients at the end of the 24 hours between each dose; the statistically significant improvement in this end point confirms the once-daily dosing interval of montelukast for PAR.

Quality-of-life measurements during treatment can complement other measurements by providing evidence of improvement in daily functioning and well-being that are important to patients. In the present study, scores for all RQLQ domains showed statistically significant improvement with montelukast therapy. Some researchers have suggested that an improvement (change from baseline) of at least 0.5 in the RQLQ score may signify an important clinical benefit.[13] Using this post hoc approach, more patients in the montelukast group than in the placebo group showed this level of improvement in RQLQ score, indicative of the beneficial effect of montelukast. A second measure of the overall change in a patient's perception of his or her clinical condition is provided by the patient's global evaluation of allergic rhinitis. A statistically significant beneficial effect with montelukast was seen in this end point. Improvements in these 2 measures, which provide an overall evaluation of patient-perceived benefit, further support the relevance of the improvements seen in the symptom scores.

In summary, this study demonstrates the benefit of the antileukotriene agent montelukast in alleviating symptoms of PAR. Statistically significant improvements were seen in diary-based end points and in patient-centered assessments. A persistent treatment effect in nasal symptoms was seen through each of the 6 weeks of treatment. These study results, along with findings from earlier studies, confirm the broad efficacy and favorable safety profile of montelukast for the treatment of symptoms of allergic rhinitis, as now demonstrated for PAR and SAR.

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Requests for reprints should be addressed to:
Piyush Patel, MD, FRCP(C)
Allied Research International
4520 Dixie Rd
Mississauga, Ontario, Canada L4W 1N2
E-mail: PPatel@allied-research.com