

Protective effect of montelukast on lower and upper respiratory tract responses to short-term cat allergen exposure

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Background: Challenge with short-term exposure to airborne cat allergen in sensitized patients produces pulmonary function changes and rhinitis symptoms.

Objective: To determine the benefit of montelukast, 10 mg, for patients with concomitant asthma and allergic rhinitis as demonstrated by protection against both lower and upper airway responses to cat allergen challenge.

Methods: This randomized, crossover study treated patients with montelukast vs placebo during two 2-week, double-blind treatment periods, separated by a 1-week washout period. After each treatment period, patients underwent a 60-minute or less exposure to high levels of airborne cat allergen. Lower and upper airway responses were measured by spirometry and symptom scores.

Results: Of 52 patients with data from both treatment arms, 79% of patients taking montelukast and 67% taking placebo were exposed to the full 60-minute allergen challenge. Montelukast provided significant ($P \leq .001$) protection against allergen challenge in the lower airway coprimary end point of area under the curve during challenge ($AUC_{0-60min}$) for percentage decrease in forced expiratory volume in 1 second: mean of 10.5% per hour and 14.7% per hour for montelukast and placebo, respectively. Although the effect on the overall nasal symptoms score (NSS) coprimary end point of $AUC_{0-60min}$ was not statistically significant ($P = .12$), nasal congestion during the challenge and NSS during recovery showed statistically significant ($P = .048$) protection by montelukast. Additional analyses of simultaneous lower and upper airway responses showed that more patients taking montelukast (22, 43%) vs placebo (13, 26%) were protected from both asthma and rhinitis ($P = .02$), with an odds ratio of 2.24 (95% CI, 1.16–4.32) in favor of montelukast.

Conclusions: Montelukast has a protective effect against both lower and upper airway responses during exposure to high levels of cat allergen.

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INTRODUCTION

Asthma and allergic rhinitis both have major clinical and socioeconomic impact due to the increasing prevalence of allergic disease¹ and their negative impact on patients' quality of life.² Asthma affects approximately 4% to 11% of the general population, whereas allergic rhinitis affects 10% to 30% of the general population.^{1,3} Additionally, asthma and allergic rhinitis are often concomitant conditions. According to several epidemiologic studies,^{4,5} 20% to 40% of patients with allergic rhinitis have asthma, whereas 30% to 90% of patients with asthma have allergic rhinitis.

A similar pathophysiology underlies asthma and allergic rhinitis. When airborne allergen affects the respiratory mu-

cosa of a sensitized patient with asthma or allergic rhinitis, airway inflammatory cells (including mast cells and eosinophils) enter an activated state to release a mixture of inflammatory mediators, including cysteinyl leukotrienes (CysLTs), histamine, and prostaglandin D₂.⁶ CysLTs are mediators of bronchoconstriction, mucous secretion, nasal congestion, and inflammatory cell influx.⁷ A specific role of CysLTs in both asthma and allergic rhinitis is supported by the recovery of these inflammatory mediators from both bronchial and nasal lavage fluid. Release of CysLTs has been documented in natural disease^{8,9} and after mucosal challenge with allergen.^{10,11} Consistent with these findings, the CysLT receptor antagonist, montelukast, has demonstrated clinical benefit in studies of persistent and acute asthma,^{12–14} asthma induced by lower airway inhalational allergen challenge with house dust mite extract,¹⁵ and seasonal allergic rhinitis.^{16–20}

We used a well-characterized cat challenge model as a means of simultaneously exposing both the lower and upper airways to an important indoor allergen. Studies involving controlled challenge with airborne cat allergen have clearly demonstrated substantial pulmonary function changes and rhinitis symptoms with short-term allergen exposure in sen-

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sitized patients.²¹ The purpose of this study was to determine the benefit of montelukast, 10 mg, in the treatment of patients with concomitant asthma and allergic rhinitis as demonstrated by protection against both lower and upper airway reactions to controlled cat allergen challenge.

METHODS

Study Design and Patients

We performed a multicenter, randomized, double-blind, crossover study. The study included 3 periods: a 2-week, double-blind treatment (period 1) followed by a 1-week washout (period 2) and a 2-week, double-blind treatment (period 3). At baseline (visit 2) and the end of each treatment period (visits 4 and 6), patients underwent cat allergen challenge for 60 minutes or less, using previously reported methods.^{22–25} Patients were administered 10-mg, film-coated tablets of montelukast or matching placebo daily in the morning on awakening during periods 1 and 3.

Patients were nonsmoking adolescents and adults who had at least a 1-year clinical history of asthma and allergic rhinitis on exposure to cats. Inclusion criteria included positive skin prick test result to cat allergen as defined by a wheal size of 3 mm or greater than diluent control; stable baseline lung function as defined by a forced expiratory volume of 1 second (FEV₁) of 70% or greater than predicted value both at study entry (visit 1) and before baseline allergen challenge (visit 2) with inhaled, short-acting β -adrenergic agonists withheld for 6 or more hours and inhaled corticosteroids withheld for 72 or more hours; and a low and stable baseline of nasal symptoms as defined by a nasal symptoms score (NSS) of 0.5 or less (of 3) at visits 1 and 2. Patients living with a cat in the home were excluded. To be eligible for randomization, patients had to demonstrate clinically relevant reactions to exposure in both pulmonary function (decrease in FEV₁ of $\geq 15\%$ from the absolute prechallenge FEV₁ value) and symptoms of allergic rhinitis (increase in NSS of ≥ 1.0 from the prechallenge score) during baseline challenge (visit 2) and had to tolerate this challenge for at least 30 minutes. For safety considerations (whether the challenge was at baseline [visit 2] or during treatment [visits 4 and 6]), patients exited the challenge before 60 minutes if they demonstrated a 50% or greater decrease from prechallenge FEV₁ or if the patient or investigator decided to terminate the challenge.

Patients with pulmonary disorders other than asthma and patients with rhinitis medicamentosa, nonallergic rhinitis, upper respiratory tract infection, sinusitis, infectious rhinitis, or ocular infection were excluded from the study. Patients using medications for allergic rhinitis, conjunctivitis, ocular or other nasal symptoms, and asthma before visits 1 or 2 were not eligible to participate in the study, and these medications were not allowed during the study with the exception of as-needed β -agonists and/or a low and stable dose of inhaled corticosteroids, defined as 400 $\mu\text{g/d}$ or less of beclomethasone dipropionate or equivalent corticosteroid regimen. The study was approved by ethical review committees for each

study site, and all patients gave written informed consent before any study procedure was performed.

End Points

The primary lung function end point was area under the curve (AUC) during the 60-minute allergen challenge (AUC_{0–60min}) for the percentage of decrease from the absolute prechallenge FEV₁. The primary nasal symptom end point was AUC for the increase from prechallenge NSS, defined as the mean scores for nasal congestion, rhinorrhea, and sneezing and rated on a 0 (none) to 3 (severe) scale during allergen challenge. These data were analyzed as coprimary end points. For the calculation of AUC_{0–60min}, the last recorded measurement was carried forward if a patient did not complete all measurements during the 60-minute challenge.

Secondary end points included (1) maximum percentage decrease from prechallenge FEV₁ during the 60-minute challenge; (2) AUC_{0–60min} for the increase from prechallenge chest symptoms score (mean of scores for wheezing and chest tightness); and (3) AUC for the increase from prechallenge NSS computed during the recovery phase, defined as the initial 30 minutes after terminating the challenge (AUC_{60–90min}), regardless of whether the challenge lasted a full 60 minutes. Additional end points measured were (1) absolute decrease in FEV₁ from prechallenge to the end of challenge; (2) AUC for the increase from prechallenge in each individual symptom of the chest symptoms score and symptom score of coughing; (3) number of coughs; (4) AUC for the increase from prechallenge in each individual symptom of the NSS and the symptom score of pruritus; (5) number of sneezes; and (6) duration of allergen exposure tolerated by the patient.

Safety and Other Measurements

Safety measurements included clinical evaluations (including physical examination), adverse experience monitoring, and laboratory safety tests. Airborne cat allergen (Fel d 1) exposure levels were measured during each challenge for each patient with a portable air filtration device worn by the patient, using previously reported methods.^{26,27}

Statistical Analysis

The primary analysis was performed using a modified intention-to-treat approach that included all patients with at least one data point from each treatment period in this crossover study. The main statistical analyses were performed using a mixed model with fixed effects of center, sequence, period, and treatment and a random effect of patient (nested within center and sequence). For the 2 coprimary end points, the change over time during the challenge was also evaluated using a repeated-model approach for the data recorded at each time point during the challenge. Data are presented as least squares means and 95% confidence intervals (CIs). Because it was originally designed for a sample size of 50 patients, the study had 98% power to detect an effect size (defined as the difference in means divided by SD) of 0.6 for the end point AUC_{0–60min} for percentage decrease in FEV₁ and 90% power

to detect an effect size of 0.47 for the end point $AUC_{0-60min}$ for increase in NSS.

In post hoc categorical analyses, a logistic regression model (with factors for treatment, center, and period) was used to examine the dual effect of treatment on the lower and upper airways. Simultaneous protection against lower and upper airway reactions was defined as showing both $AUC_{0-60min}$ for percentage of decrease in FEV_1 of less than 10% per hour and $AUC_{0-60min}$ for increase in NSS of less than 1.0 score per hour. These cutoff values for each coprimary end point were chosen to approximate the observed median values of $AUC_{0-60min}$ for percentage decrease in FEV_1 of 9.5% per hour and $AUC_{0-60min}$ for increase in NSS of 0.8 score per hour. The between-treatment comparisons of duration of allergen exposure were performed by the Wei, Lin, and Weissfeld method of regression for multivariate censored data.²⁸ Recovery from challenge, evaluated during the 30-minute recovery phase, was defined for the lower airway as an FEV_1 within at least 95% of the prechallenge FEV_1 and for the upper airway as an NSS less than 0.5. Time to recovery in NSS was evaluated in post hoc analyses using the Wei, Lin, and Weissfeld model.

RESULTS

Of 130 patients screened for inclusion in the study, 72 patients were excluded and not randomized, 58 were randomized, and 52 completed the study. Thirty-three patients did not qualify for randomization due to insufficient nasal symptoms or FEV_1 change in their baseline challenge. Clinical and demographic characteristics of the patients are given in Table 1. The mean age was 31 years, and approximately two thirds of the enrolled patients were women. All had a history of allergic rhinitis and 97% had a history of asthma. Baseline challenge data for the coprimary end points and selected secondary end points for all randomized patients are given in Table 2. The mean prechallenge FEV_1 was 93.1% of predicted, and the mean maximum decrease in FEV_1 from pre-

Table 2. Baseline Challenge (Visit 2) Data for Selected End Points: Prechallenge and Response to Challenge

Data at baseline challenge	Mean $\pm$ SD
Prechallenge	
FEV_1 (% predicted)	93.1 $\pm$ 15.0
NSS	0.17 $\pm$ 0.21
Chest symptoms score	0.10 $\pm$ 0.20
Response to challenge	
$AUC_{0-60min}$ for decrease in FEV_1 , %/h	16.7 $\pm$ 9.2
Maximum decrease in FEV_1 , %	38.2 $\pm$ 13.6
$AUC_{0-60min}$ for increase in NSS, score per hour	1.22 $\pm$ 0.42
AUC during challenge for increase in chest symptom score, score per hour	1.38 $\pm$ 0.55
Duration of challenge, min	45.4 $\pm$ 12.8

Abbreviations: $AUC_{0-60min}$, area under the curve during the 60-minute allergen challenge; FEV_1 , forced expiratory volume in 1 second. NSS, nasal symptoms score.

challenge was 38.2%. For challenges performed at the end of each treatment period, the prechallenge values were similar to each other and to the prechallenge values at the baseline challenge.

Efficacy in Lower Airway End Points

Montelukast, compared with placebo, demonstrated statistically significant ($P \leq .001$) protection against allergen challenge in the lower airway primary end point, $AUC_{0-60min}$ for percentage decrease in FEV_1 (Fig 1), with a mean value of 10.5% per hour (95% CI, 7.5%–13.4%) for patients taking montelukast and 14.8% per hour (95% CI, 11.8%–17.7%) for patients taking placebo. Montelukast also demonstrated significant protection ($P \leq .001$) for the maximum decrease in FEV_1 during the 60-minute challenge, with a mean decrease of 19.3% (95% CI, 14.7%–23.6%) for patients taking montelukast and 26.5% (95% CI, 21.8%–30.8%) for patients

Table 1. Patient Demographics and Characteristics

Variable	Finding (N = 58)
Demographics	
Age, mean $\pm$ SD (range), y	31.0 $\pm$ 9.2 (18–53)
Female, No. (%)	40 (69)
Race, No. (%)	
White	40 (69)
Other	18 (31)
Allergic history	
History of allergic rhinitis, No. (%)	58 (100)
History of asthma, No. (%)	56 (97)
History of allergic conjunctivitis, No. (%)	53 (91)
History of eczematous dermatitis, No. (%)	10 (17)
Duration of asthma, mean $\pm$ SD, y	19.4 $\pm$ 9.2
Duration of allergic rhinitis, mean $\pm$ SD, y	17.2 $\pm$ 8.9
Duration of allergic conjunctivitis, mean $\pm$ SD, y	19.9 $\pm$ 9.0

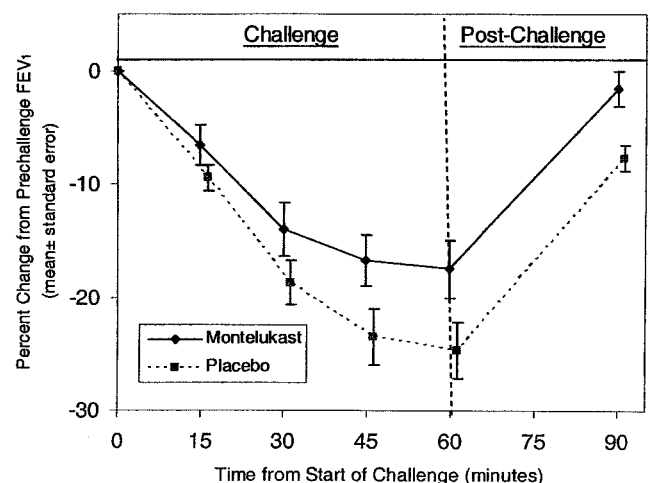


Figure 1. Percentage decrease from prechallenge forced expiratory volume in 1 second (FEV_1) during (0 to 60 minutes) and after (60 to 90 minutes) controlled cat allergen challenge.

taking placebo. Similarly, the montelukast treatment effect on the absolute decrease in FEV₁ from prechallenge to the end of challenge was statistically significant ($P \leq .001$) compared with placebo (Table 3), with mean values of 0.56 L (95% CI, 0.39–0.71 L) for patients taking montelukast and 0.80 L (95% CI, 0.64–0.95 L) for patients taking placebo.

The AUC_{0–60min} for the increase from prechallenge chest symptoms score was lower with montelukast (mean, 0.70 score per hour; 95% CI, 0.53–0.86 score per hour) compared with placebo (mean, 0.80 score per hour; 95% CI, 0.63–0.96 score per hour), although the difference was not statistically significant ($P = .23$; Table 3). The effect of montelukast showed a similar trend on other end points (AUC for the increase from prechallenge in the individual chest symptoms of wheezing and chest tightness, coughing score, and number of coughs during the 60-minute challenge), but none of these differences was statistically significant (Table 3).

Efficacy in Upper Airway End Points

There was a trend toward a reduction with montelukast on the upper airway primary end point, AUC_{0–60min} for increase in NSS, with a mean value of 0.80 score per hour (95% CI, 0.67–0.95 score per hour) for patients taking montelukast compared with 0.92 score per hour (95% CI, 0.78–1.06 score per hour) for patients taking placebo ($P = .12$; Table 4). An additional analysis of the increases in NSS during the 60-minute challenge was performed using a repeated-model approach; the difference between treatment groups in average increase in NSS during the 60-minute challenge showed borderline statistical significance ($P = .07$).

The benefit of montelukast on nasal symptoms during the recovery phase of 30 minutes after terminating challenge was statistically significant ($P = .04$; Table 4) as measured by the secondary end point of AUC_{60–90min} for increase in NSS: mean value of 0.29 score per hour (95% CI, 0.21–0.37 score per hour) for patients taking montelukast and 0.37 score per hour (95% CI, 0.29–0.45 score per hour) for patients taking placebo. For the combined periods of challenge and postchallenge recovery (0–90 minutes), montelukast was borderline statistically significant ($P = .07$) in protecting against an increase in the AUC_{0–90min} for increase in NSS.

For the specific symptom of nasal congestion, montelukast showed a significant ($P = .048$) benefit during the challenge as measured by the secondary end point of AUC_{0–60min} for the increase from prechallenge (Table 5). The effect of montelukast on nasal congestion during the 30-minute recovery phase (AUC_{60–90min}) showed borderline statistical significance ($P = .09$) compared with placebo. The effects of montelukast on the other individual nasal symptoms (rhinorrhea, sneezing, and pruritus) and in the number of sneezes showed a similar trend, but none of the differences was statistically significant (Table 5), except for the effect on rhinorrhea during the recovery phase ($P = .045$).

Dual Effect of Montelukast Treatment

Using a post hoc categorical analysis, patients taking montelukast, compared with placebo, were protected from a decrease in lung function ($P = .02$) and an increase in nasal symptoms ($P = .04$) during the challenge (Fig 2). Significantly more patients taking montelukast ($P = .02$) showed dual protection from both asthma and rhinitis (Fig 2), since 22 patients (43%) taking montelukast and 13 patients (25%) taking placebo simultaneously met the criteria for lower and upper airway protection (odds ratio, 2.24; 95% CI, 1.16–4.32).

Other Analyses

Of the 52 patients, 11 (21%) taking montelukast and 17 (33%) taking placebo did not tolerate the entire challenge and exited before achieving an allergen exposure of 60 minutes, leaving 79% of patients taking montelukast and 67% taking placebo who were exposed to the full 60-minute allergen challenge. The mean duration of exposure to allergen was 56 minutes for patients taking montelukast and 51 minutes for patients taking placebo (hazard reduction, 41%; $P = .09$). The number of patients who exited challenge before 60 minutes and their duration of challenge are shown in Figure 3.

Recovery from challenge was evaluated by analyzing lower and upper airway responses during the 30-minute postchallenge period. Thirty-seven patients (75%) taking montelukast, compared with 24 patients (49%) taking placebo,

Table 3. Secondary and Additional Lower Airway End Points: Differences between Montelukast and Placebo*

	Challenge period (0–60 minutes)		Postchallenge period (60–90 minutes)	
	Mean difference (95% CI)	P value	Mean difference (95% CI)	P value
Maximum decrease in FEV ₁ , % decrease during challenge	–7.2 (–10.9 to –3.5)	$\leq .001$	...	...
Prechallenge FEV ₁ to end of challenge, L	–0.25 (0.11 to 0.38)	$\leq .001$	...	...
AUC increase in chest symptoms score, score per hour	–0.10 (–0.26 to 0.06)	.23	–0.04 (–0.11 to 0.04)	.32
AUC increase in wheezing score, score per hour	–0.14 (–0.31 to 0.04)	.12	–0.06 (–0.15 to 0.03)	.17
AUC increase in chest tightness score, score per hour	–0.08 (–0.26 to 0.09)	.35	–0.03 (–0.13 to 0.07)	.57
AUC increase in coughing score, score per hour	–0.07 (–0.26 to 0.11)	.44	–0.02 (–0.07 to 0.04)	.52
No. of coughs per hour	–6.6 (–23.8 to 10.7)	.45	–2.4 (–4.7 to –0.1)	.04

Abbreviations: AUC, area under the curve; CI, confidence interval; FEV₁, forced expiratory volume in 1 second.

* Differences are provided as least squares mean values; negative differences favor montelukast.

Table 4. Change from Prechallenge Nasal Symptoms Score during and after Controlled Cat Allergen Challenge*

	Challenge period (0–60 minutes)		Postchallenge period (60–90 minutes)		Challenge and postchallenge periods combined (0–90 minutes)	
	Mean difference (95% CI)	P value	Mean difference (95% CI)	P value	Mean difference (95% CI)	P value
AUC increase in nasal symptoms score, score per hour	−0.11 (−0.25 to 0.03)	.12	−0.07 (−0.15 to −0.00)	.04	−0.19 (−0.39 to 0.02)	.07

Abbreviations: AUC, area under the curve; CI, confidence interval.

* Differences between montelukast and placebo are shown as least squares mean values, with negative differences favoring montelukast.

Table 5. Secondary and Additional Upper Airway End Points: Differences between Montelukast and Placebo*

	Challenge period (0–60 minutes)		Postchallenge period (60–90 minutes)	
	Mean difference (95% CI)	P value	Mean difference (95% CI)	P value
AUC increase in nasal congestion, score per hour	−0.17 (−0.34 to −0.00)	.048	−0.09 (−0.19 to 0.01)	.09
AUC increase in rhinorrhea, score per hour	−0.13 (−0.32 to 0.05)	.15	−0.10 (−0.19 to −0.00)	.045
AUC increase in sneezing, score per hour	−0.03 (−0.16 to 0.10)	.63	−0.04 (−0.09 to 0.00)	.07
AUC increase in pruritus, score per hour	−0.09 (−0.28 to 0.10)	.35	−0.05 (−0.14 to 0.04)	.29
No. of sneezes per hour	0.80 (−0.54 to 2.28)	.22	−0.23 (−0.77 to 0.31)	.40

Abbreviations: AUC, area under the curve; CI, confidence interval.

* Differences are provided as least squares mean values; negative differences favor montelukast.

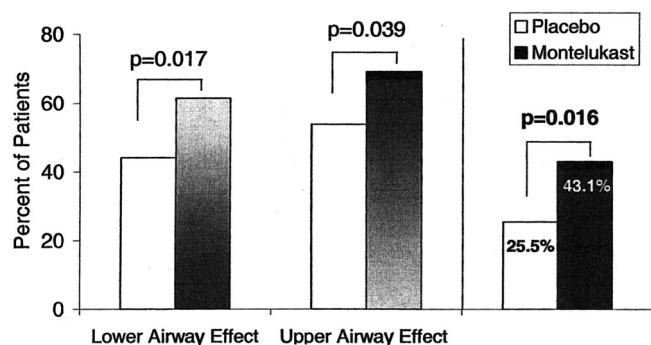


Figure 2. Dual effect of montelukast on the lower airway effect (area under the curve [AUC] for percentage decrease in forced expiratory volume in 1 second of <10% per hour) and upper airway effect (AUC for increase in nasal symptoms score of <1.0 score per hour) by categorical analysis: percentage of patients protected from a more severe reaction during allergen challenge.

demonstrated lower airway recovery within 30 minutes after challenge, defined as an FEV₁ level within at least 95% of the prechallenge FEV₁ level ($P = .002$). Similarly, 40 patients (82%) taking montelukast, compared with 33 patients (67%) taking placebo, demonstrated upper airway recovery, defined as a postchallenge NSS level of less than 0.5; time to recovery for NSS showed a significant benefit for patients taking montelukast ($P = .02$).

The median Fel d 1 level recorded during challenge (periods 1 and 3) was 634 ng/m³ (range, 94–5,709 ng/m³) for

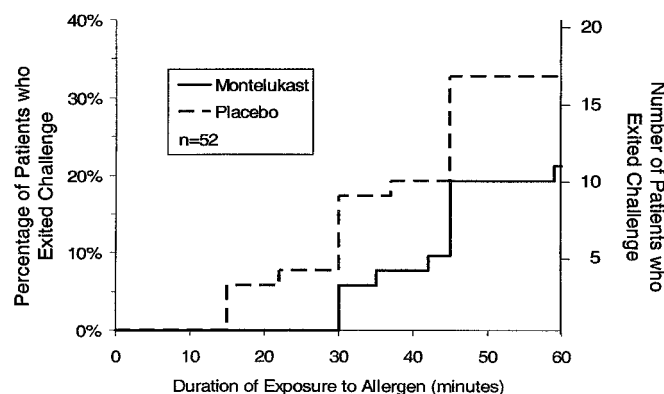


Figure 3. Patients who exited the cat allergen challenge before 60 minutes.

patients taking montelukast and 437 ng/m³ (range, 51–13,201 ng/m³) for patients taking placebo. Estimates of the treatment effect for the upper and lower airway primary end points were also derived from a model that incorporated Fel d 1 level as covariate. Although airborne levels were highly variable, analysis using Fel d 1 levels yielded results similar to those obtained from the main analysis model. The treatment effect was consistent across the 2 study centers, and no sequence effect was detected.

Safety

There were no clinically meaningful differences in adverse experiences reported during montelukast vs placebo treat-

ment periods. No adverse experiences were considered drug related by the investigators.

DISCUSSION

There is general recognition that asthma and allergic rhinitis are systemically linked by integrated inflammatory processes of the upper and lower airways,²⁹ thus leading to the concept of “one-airway, one disease.”³⁰ Our current understanding of the shared pathophysiology, health impairments, and socioeconomic costs of asthma and allergic rhinitis has culminated in the Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines, which recommend a therapeutic approach that combines the treatment of both upper and lower airways.³¹

Corticosteroid therapy is often effective for asthma and allergic rhinitis. However, because of adverse effects associated with systemic corticosteroids, this therapy is usually topical and requires separate administration of an inhaled corticosteroid for asthma and an intranasal corticosteroid for allergic rhinitis. Oral antihistamines are widely used for allergic rhinitis but are not approved for the treatment of asthma. Other than systemic corticosteroids, there have been no oral agents indicated for the treatment of both asthma and allergic rhinitis. For the large patient population with concomitant asthma and allergic rhinitis, it would be clinically advantageous to treat both conditions with a single, effective, and well-tolerated oral agent that targets the systemic inflammatory process underlying both conditions. In this regard, a number of recent articles have advocated a role for CysLT antagonists in the treatment of comorbid allergic rhinitis and asthma.^{30,32,33}

The cat allergen model has been used previously to examine the effects of a variety of antiallergic agents, including antileukotrienes and intranasal corticosteroids. Phipatanakul and colleagues²⁵ showed that montelukast significantly decreased lower respiratory responses and extended challenge duration in cat-sensitive children with mild persistent asthma. Similarly, zafirlukast, another antileukotriene, was effective in preserving pulmonary function in adults with cat-sensitive asthma.^{23,24} Effects of intranasal triamcinolone were examined in both the upper and lower airway; although differences from placebo on nasal symptoms were not statistically significant, there was a significant protection by intranasal triamcinolone in lower airway symptoms,²² supporting the “one-airway” concept.

Although previous studies measured upper airway effects, this study is the first specifically designed to use the cat allergen challenge model to evaluate patients with confirmed allergic responses in both the lower and upper airways. During the baseline allergen challenge, patients were required to demonstrate a decrease of 15% or more of the absolute prechallenge FEV₁ value and an increase in NSS of 1.0 or more from the prechallenge score. Other studies have been designed primarily to evaluate lung function in response to cat allergen exposure, such that a significant decrease in lung function was required at baseline, but significant nasal symptoms were not. Nevertheless, exploration of nasal responses

has suggested that upper airway symptoms and objective nasal obstruction in this model could be significantly reduced by an antileukotriene.²⁴

The results of our study confirm that montelukast protects lung function in cat-sensitive asthmatic patients exposed to naturally generated airborne cat allergen. There was a significant protection in a number of FEV₁ parameters: AUC_{0–60min} for percentage decrease in FEV₁, the primary lung function end point, which measures the extent and duration of reduced lung function; the maximum percentage decrease from the absolute prechallenge FEV₁ during challenge; and the absolute decrease in FEV₁ from prechallenge to the end of challenge. Additional subjective end points relating to chest symptoms and coughing showed numerical (although not statistical) improvement with montelukast compared with placebo. This lack of a close relationship between objective measures of lung function and subjective measures of chest symptoms has been noted in a number of other asthma studies.^{34–36}

Upper airway symptoms showed trends toward improvement in all nasal end points in patients receiving montelukast, with statistical differences from placebo in nasal congestion during challenge and the NSS and rhinorrhea during the 30-minute postchallenge recovery period. The significant effect of montelukast on the symptom of nasal congestion during the challenge is consistent with a previously reported effect of montelukast on congestion as measured by acoustic rhinometry.²⁴

A unique aspect of the design and results of this study was the demonstration of dual effects of montelukast as measured by the primary end points for the lower and upper airways. The cat allergen challenge model allows evaluation of lower and upper airway reactions in patients who demonstrate simultaneous “cat asthma” and “cat rhinitis” in response to inhaled allergen challenge. However, very high levels of allergen are used in this short-term challenge model system; airborne levels of Fel d 1 in this study (range, 51–13,201 ng/m³) were 10-fold higher than those that were found in homes with cats in a previous study (range, 1.8–578 ng/m³).³⁷ Consequently, levels of clinical reactions in this challenge model may not relate easily to expected levels of clinical reactions to cat exposure in homes. On the other hand, airborne allergen levels are known to be highly variable in this model^{22–26}; thus, it is not clear if a linear relationship exists between airborne allergen levels and the reactions induced or duration of challenge tolerated. Levels of lower and upper airway protection were therefore defined based on the median responses observed in this model system for each primary end point. Using this approach, montelukast demonstrated significant protection from a simultaneous lower and upper airway reaction, such that patients taking montelukast were approximately twice as likely to be protected from inhaled cat allergen when taking montelukast compared with placebo.

Although the results of this study are generally indicative of a positive effect of an antileukotriene on lower and upper airway allergic responses, the overall effects of this treatment

may have been underestimated. Patients in this study (who did not live with a cat in the home) were exposed to very high levels of cat allergen. This may have overwhelmed some of the treatment effect and may have made it harder for patients to detect differences in their subjective evaluation of upper and lower airway symptoms. Additionally, more patients exited the challenge before 60 minutes when receiving the placebo treatment; had these challenges on placebo lasted longer, the nasal symptoms (and other measures) could have been greater with placebo, and the corresponding differences from montelukast might also have been greater.

In summary, the results of this study indicate that montelukast has a protective effect against lower and upper airway responses to short-term allergen exposure. Furthermore, the study suggests that in patients with clinically significant responses in both the lower and upper airway to cat allergen, montelukast has a simultaneous and dual protective effect against both lung function and nasal symptom reactions to short-term allergen exposure. Additional studies, particularly with more naturally relevant levels of airborne allergen, may provide further support for the use of a single agent such as montelukast for the treatment of the comorbid diseases of asthma and allergic rhinitis.

REFERENCES

1. Von Mutius E. The rising trends in asthma and allergic disease. *Clin Exp Allergy*. 1998;28:45–49.
2. Leynaert B, Neukirch C, Liard R, Bousquet J, Neukirch F. Quality of life in allergic rhinitis and asthma: a population-based study of young adults. *Am J Respir Crit Care Med*. 2000;162:1391–1396.
3. Nathan RA, Meltzer EO, Selner JC, Storms W. Prevalence of allergic rhinitis in the United States. *J Allergy Clin Immunol*. 1997;99:S808–S814.
4. Simons FE. Allergic rhinobronchitis: the asthma-allergic rhinitis link. *J Allergy Clin Immunol*. 1999;104:534–540.
5. Leynaert B, Neukirch F, Demoly P, Bousquet J. Epidemiologic evidence for asthma and rhinitis comorbidity. *J Allergy Clin Immunol*. 2000;106(Suppl):S201–S205.
6. Naclerio RM. Allergic rhinitis. *N Engl J Med*. 1991;325:860–869.
7. Sampson AP, Pizzichini E, Bisgaard H. Effects of cysteinyl leukotrienes and leukotriene receptor antagonists on markers of inflammation. *J Allergy Clin Immunol*. 2003;111:S49–S59.
8. Lam S, Chan H, LeRiche JC, Chan-Yeung M, Salari H. Release of leukotrienes in patients with bronchial asthma. *J Allergy Clin Immunol*. 1988;81:711–717.
9. Volovitz B, Osur SL, Bernstein JM, Ogra PL. Leukotriene C₄ release in upper respiratory mucosa during natural exposure to ragweed in ragweed-sensitive children. *J Allergy Clin Immunol*. 1988;82:414–418.
10. Liu MC, Hubbard WC, Proud D, et al. Immediate and late inflammatory responses to ragweed antigen challenge of the peripheral airways in allergic asthmatics: cellular, mediator, and permeability changes. *Am Rev Respir Dis*. 1991;144:51–58.
- 11.CRETICOS PS, Peters SP, Adkinson NF Jr, et al. Peptide leukotriene release after antigen challenge in patients sensitive to ragweed. *N Engl J Med*. 1984;310:1626–1630.
12. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg B, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. *Arch Intern Med*. 1998;158:1213–1220.
13. Reiss TF, Knorr B, Malmstrom K, et al. Clinical efficacy of montelukast in adults and children. *Clin Exp Allergy Rev*. 2001;1:264–273.
14. Camargo CA Jr, Smithline HA, Malice MP, Green SA, Reiss TF. A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med*. 2003;167:528–533.
15. Diamant Z, Grootendorst DC, Veselic-Charvat M, et al. The effect of montelukast (MK-0476), a cysteinyl leukotriene receptor antagonist, on allergen-induced airway responses and sputum cell counts in asthma. *Clin Exp Allergy*. 1999;29:42–51.
16. Meltzer EO, Malmstrom K, Lu S, 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.
17. Nayak AS, Philip G, Lu S, Malice MP, 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.
18. Philip G, Malmstrom K, Hampel FC Jr, et al; Montelukast Spring Rhinitis Study Group. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy*. 2002;32:1020–1028.
19. van Adelsberg J, LaForce CF, Weinstein SF, et al. Randomized controlled trial evaluating clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol*. 2003;90:214–222.
20. van Adelsberg J, Philip G, Pedinoff AJ, et al. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy*. 2003;58:1268–1276.
21. Chapman MD, Wood RA. The role and remediation of animal allergens in allergic diseases. *J Allergy Clin Immunol*. 2001;107:S414–S421.
22. Wood RA, Eggleston PA. The effects of intranasal steroids on nasal and pulmonary responses to cat exposure. *Am J Respir Crit Care Med*. 1995;151:315–320.
23. Corren J, Spector S, Fuller L, Minkwitz M, Mezzanotte W. Effects of zafirlukast upon clinical, physiologic, and inflammatory responses to natural cat allergen exposure. *Ann Allergy Asthma Immunol*. 2001;87:211–217.
24. Phipatanakul W, Eggleston PA, Conover-Walker MK, Kesavananathan J, Sweitzer D, Wood RA. A randomized, double-blind, placebo-controlled trial of the effect of zafirlukast on upper and lower respiratory responses to cat challenge. *J Allergy Clin Immunol*. 2000;105:704–710.
25. Phipatanakul W, Nowak-Wegrzyn A, Eggleston PA, et al. The efficacy of montelukast in the treatment of cat allergen-induced asthma in children. *J Allergy Clin Immunol*. 2002;109:794–799.
26. Wood RA, Laheri AN, Eggleston PA. The aerodynamic characteristics of cat allergen. *Clin Exp Allergy*. 1993;23:733–739.
27. Chapman MD, Aalberse RC, Brown MJ, Platts-Mills TA. Monoclonal antibodies to the major feline allergen Fel d I: single-step affinity purification of Fel d I, N-terminal sequence analysis, and development of a 2-site immunoassay to assess Fel d I exposure. *J Immunol*. 1988;140:812–818.

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28. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by modeling marginal distributions. *J Am Stat Assoc.* 1989;84:1065–1073.
29. Togias A. Rhinitis and asthma: evidence for respiratory system integration. *J Allergy Clin Immunol.* 2003;111:1171–1183.
30. Canonica GW. Evaluation and management of patients with asthma and allergic rhinitis: exploring the potential role for leukotriene receptor antagonists. *Clin Exp Allergy Rev.* 2003;3: 61–62.
31. 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: S147–S334.
32. Dahlen SE. Cysteinyl leukotrienes as common mediators of asthma and allergic rhinitis. *Clin Exp Allergy Rev.* 2003;3: 69–73.
33. Pawankar R. Exploring the role of leukotriene receptor antagonists in the management of allergic rhinitis and comorbid asthma. *Clin Exp Allergy Rev.* 2003;3:74–80.
34. Atherton HA, White PT, Hewett G, Howells K. Relationship of daytime asthma symptom frequency to morning peak expiratory flow. *Eur Respir J.* 1996;9:232–236.
35. Shingo S, Zhang J, Reiss TF. Correlation of airway obstruction and patient-reported endpoints in clinical studies. *Eur Respir J.* 2001;17:220–224.
36. Zhang J, Yu C, Holgate ST, Reiss TF. Variability and lack of predictive ability of asthma end-points in clinical trials. *Eur Respir J.* 2002;20:1102–1109.
37. Bollinger MB, Eggleston PA, Johnson EF, Wood RA. Cat antigen in homes with and without cats may induce allergic symptoms. *J Allergy Clin Immunol.* 1996;97:907–914.
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