
Effects of zafirlukast upon clinical, physiologic, and inflammatory responses to natural cat allergen exposure

Jonathan Corren, MD*; Sheldon Spector, MD*; Lara Fuller, RN*; Margaret Minkwitz, PhD†; and William Mezzanotte, MD†

Background: Leukotriene receptor antagonists have been shown to attenuate physiologic changes in the upper and lower airways induced by allergen challenge. However, it is unknown whether these drugs modulate airway inflammation after exposure to allergen in a natural setting.

Objective: To determine the effects of the oral leukotriene receptor antagonist zafirlukast upon symptoms, changes in pulmonary function, and indices of inflammation in the upper and lower airways induced by natural exposure to cats.

Methods: Zafirlukast, 20 mg twice daily, or placebo was administered to 18 cat-allergic asthmatic patients in this randomized, double-blind, crossover study. Cat room challenges were performed after a 1-week period of each treatment. Upper and lower airway symptoms were measured and spirometry performed before and at regular intervals during each challenge. Nasal lavage and sputum induction were performed 24 hours before and after each challenge.

Results: Zafirlukast significantly improved the prechallenge baseline FEV₁ ($P = 0.001$) and attenuated the decrease in FEV₁ induced by cat challenge ($P = 0.019$). Zafirlukast also significantly reduced lower airway symptoms associated with cat challenge ($P = 0.005$) but had no effects on nasal symptoms. Although zafirlukast did not significantly differ from placebo in its effects on sputum inflammatory cells or eosinophil cationic protein, it significantly reduced the absolute counts of total white cells, lymphocytes, neutrophils, and basophils in nasal lavage fluid.

Conclusions: Zafirlukast, 20 mg twice daily for 1 week, demonstrated a significant protective effect on symptoms of asthma and alterations in pulmonary function induced by natural cat exposure, whereas nasal symptoms and markers of sputum inflammation were not affected by the medication.

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INTRODUCTION

Symptoms of cat allergy occur commonly in the United States.¹ Because avoidance of exposure may be difficult for many allergic patients, cat-induced rhinitis and asthma are usually treated

with pharmacologic therapies, including intranasal and inhaled corticosteroids, cromone compounds, and antihistamines. Although many of these drugs have been shown to attenuate allergic reactions in the nose and chest after nebulized allergen challenge,^{2–5} it is unclear whether this type of experimental model predicts efficacy during natural exposures.

Because natural cat exposure uses a naturally generated allergen and both the upper and lower airways are exposed simultaneously, it may offer a more relevant model of allergic disease than nebulized allergen provocation. It is also ideally suited for studying treatments that affect both the nose and chest.

Zafirlukast (AstraZeneca Pharmaceuticals, Wilmington, DE) is an oral leukotriene D₄ receptor antagonist shown to be effective for the treatment of patients with mild-to-moderate asthma. In bronchial challenge studies, zafirlukast significantly attenuated both early and late asthmatic responses to laboratory allergen challenge^{5,7–8} and more recently reduced the pulmonary response to cat room challenge.⁹ Although zafirlukast did not inhibit sputum eosinophilia when administered at an approved dose,¹⁰ it significantly reduced lymphocytes and basophils in bronchoalveolar lavage (BAL). In addition, although there is some evidence that leukotriene modifiers may reduce symptoms of rhinitis,^{7,11} it is uncertain whether these agents have any effects on nasal inflammation. Therefore, this study attempted to determine the effects produced by zafirlukast, 20 mg twice daily, on clinical, physiologic, and inflammatory responses of the upper and lower airways to natural cat allergen exposure.

METHODS

Subjects

Nonsmoking men and women aged 12 to 65 years were eligible for the study. Subjects were required to have a history of cat allergen-induced rhinitis and asthma for at least 2 years, a positive skin prick test response (>3 mm wheal diameter) to full-strength standardized cat allergen extract (100,000 allergy units per mL, Greer Laboratories, Lenoir, NC), and a positive response to a screening cat room challenge. At the time of study entry, subjects had to be free of nasal and lower respiratory symptoms, have an forced expiratory volume in 1 second

* Allergy Research Foundation, Inc, Los Angeles, California.

† AstraZeneca Pharmaceuticals, Wilmington, Delaware.

The current affiliation for Dr. Spector is California Allergy & Asthma Medical Group, Los Angeles, California.

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(FEV₁) >70% of predicted value, and be receiving no medications for rhinitis or asthma on a regular basis. Subjects were excluded if they had nasal diseases other than allergic rhinitis that resulted in nasal obstruction; pulmonary diseases other than asthma; an upper respiratory infection within 6 weeks of study entry; or clinically significant abnormalities of screening laboratory tests. All subjects provided statements of informed consent before study entry, and the study protocol was approved by the Western Institutional Review Board.

Cat Room Challenge

All cat challenges were performed in a 50-m³ room furnished with wall-to-wall carpeting, one upholstered chair, one futon bed with overlying sheet, and one cat litter box. The door, windows, and ventilation system were closed most of the time, and the room was swept once weekly. Two neutered adult cats (one male and one female) lived in the room at all times and were free to move about except during challenges, at which time they were placed in two wire cages. Concentrations of cat dander (*Fel d 1*) sampled on a weekly basis during the past year ranged between approximately 500 ng/m³ and 1,200 ng/m³.

Before all cat challenges, medications were withheld as follows: antihistamines for 72 hours (except for astemizole, which was excluded for 90 days); inhaled β -agonists for 6 hours; ipratropium bromide for 12 hours; salmeterol for 48 hours; theophylline for 48 hours; nasal or inhaled cromolyn or nedocromil sodium for 28 days; leukotriene modifiers for 28 days; and inhaled, oral, or parenteral corticosteroids for 28 days. Immediately before challenge, the cats were placed in their cages, the room ventilation was turned off, the futon sheet was shaken vigorously to distribute cat allergen throughout the room, and subjects were clothed in disposable hospital gowns to protect their clothing from cat allergen. Before subjects entered the challenge room, baseline upper

(nasal congestion, rhinorrhea, pruritus) and lower (chest tightness, wheezing) respiratory symptoms were recorded using a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, and 3 = severe) and spirometry (Koko spirometer, PDS Instrumentation, Louisville, CO) and peak expiratory flow rate (PEFR) meter (Mini-Wright, Clement Clark, Inc, Columbus, OH) were performed in triplicate, with the best of three measurements recorded.

During the challenge, symptoms were recorded every 5 minutes and subjects exited the challenge room every 10 minutes so that spirometry could be performed and PEFR measured. After challenge, two puffs of albuterol were administered by metered-dose inhaler if the subject felt it was necessary. Given that the majority of patients received albuterol at the end of challenge, the occurrence of late-phase reactions may have been affected. After being discharged from the cat challenge room, subjects measured PEFR every 2 hours for 12 hours.

Allergen exposure was measured throughout the challenge procedure using a portable air filtration device, with the intake port attached to the subject's shoulder. The filtration pump (Gillian Instrument Corp, Wayne, NJ) was calibrated to a flow rate of approximately 4 L/minute. Cat antigen was collected on 25-mm round glass-fiber filters (Millipore Corp., Bedford, MA) contained in plastic cassettes, which were frozen at -20°C *Fel d 1* concentration was measured with a two-site antibody-based ELISA. The airborne concentration of *Fel d 1* was expressed as nanograms of allergen per cubic meter of sampled air.

Collection and Processing of Nasal Lavage and Sputum Samples

Nasal Lavage. Five sequential 10 mL aliquots of normal saline were instilled into the nose, and aliquots 2 to 5 were pooled for analysis.¹² After centrifugation at 350 *g* for 10 minutes, the supernatant was removed and stored at -70 °C for later analysis of eosinophil cationic protein (ECP). The resuspended cell pellet was examined for to-

tal cell count, and the remainder was centrifuged using a Cytospin (Shandon Scientific, Sewickley, PA) at 600 rpm for 6 minutes. After drying, the slide was stained with May-Grünwald-Giemsa stain for differential count. Two independent technicians each counted at least 200 cells, and the average count was used for analysis.

Sputum Induction. After receiving four puffs of albuterol, subjects underwent six consecutive 2-minute periods of nebulization with 3% saline (DeVilbiss Ultra-Neb 99 ultrasonic nebulizer, Sunrise Medical, Somerset, PA).¹³ After each nebulization, coughed sputum was collected for analysis. The pooled sample was diluted with an equal volume of dithiothreitol 10% (Sputalysin, Behring Diagnostic, Inc., Westwood, MA), and the resultant homogenized sample was examined for total cell count. After centrifugation at 1,500 rpm for 5 minutes, the cell pellet was cytocentrifuged for differential count and the supernatant frozen for later ECP analysis.

ECP concentrations in homogenized sputum and nasal lavage supernate were measured using a commercial radioimmunoassay kit (Pharmacia Diagnostics, Inc, Fairfield, NJ).

Study Design

The study used a randomized, double-blind, placebo-controlled crossover design (Fig 1). After enrollment in the study, subjects underwent a screening cat challenge as described earlier. The screening challenge was terminated when FEV₁ decreased by at least 15% from baseline value. The time required to reach this 15% reduction in FEV₁ was established as the provocative time, which was used throughout the study.

Fourteen days after the screening challenge, subjects were assigned at random to receive either zafirlukast, 20 mg twice daily, or placebo for 7 consecutive days. On day 6 of the treatment period, subjects underwent prechallenge sputum induction and nasal lavage. On the morning of day 7, subjects underwent a second cat challenge 2 hours after their last dose of study medication, with the challenge dura-

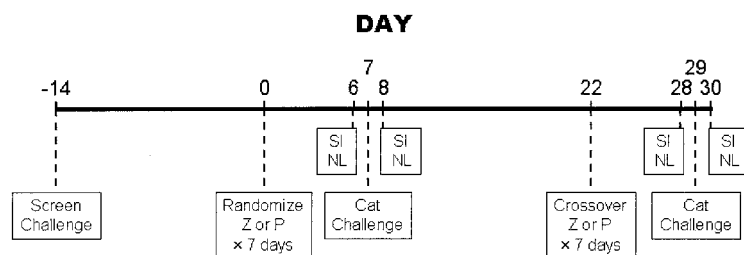


Figure 1. Study design. Z, zafirlukast, 20 mg twice daily; P, placebo; SI, sputum induction; NL, nasal lavage.

tion determined by the previous provocation time. Twenty-four hours later, on day 8, subjects underwent post-challenge sputum induction and nasal lavage. After completing the first treatment period, subjects underwent a 14-day washout period and were then crossed over to receive the alternate therapy during the second treatment period. On days 6, 7, and 8 of treatment period 2, all procedures occurred as described previously for treatment period 1.

Statistical Methods

Principal outcome measures evaluated included the maximum decrease in FEV₁, immediate postchallenge FEV₁, and PEFR; individual and composite scores for upper and lower airway symptoms; decrease in PEFR, both the maximum and area under the curve (AUC) measured immediately postchallenge to 12 hours after challenge; incidence of late asthmatic reactions, defined as $\geq 15\%$ drop in PEFR from baseline at one timepoint between 4 and 12 hours after cat challenge; and cell counts and ECP measured from induced sputum and nasal lavage fluid. An ANOVA model was used for the immediate postchallenge and maximum decreases in FEV₁ and PEFR, PEFR-AUC during the 12-hour postchallenge period, and upper and lower airway symptom scores. To evaluate nasal and sputum cellular changes, data were first transformed because of a failure of assumptions. An ANCOVA model was then used for the rank-transformed nasal lavage and sputum data, with day 6 prechallenge data serving as baseline.

RESULTS

Subject Characteristics

Eighteen subjects (9 men and 9 women) completed the study (Table 1). The mean age was 28.5 years and the mean duration of asthma was 21.2 years. The mean FEV₁ evaluated during the screening period was 85.3% of predicted value, with a range between 73% to 102% of predicted value. All patients had a history of asthma symptoms after cat exposure. The duration of cat exposure required to cause a 15% or greater decrease in FEV₁ at screening was 10 minutes for 6 patients and 20 minutes for 12 patients, with a median decrease in FEV₁ of 23.1%.

Fel d 1 Measurements

Average exposure to cat allergen was similar across treatment periods, with a mean *Fel d 1* concentration of 1,029 ng/m³ for zafirlukast and 981 ng/m³ for placebo (Fig 2). Although there were large differences in *Fel d 1* concentrations between the two challenge days

in 5 of 18 subjects, no relation was detected between any of the outcome variables and level of allergen exposure. Excluding patients who had a greater than 1 log shift in *Fel d 1* concentration yielded results similar to that observed in the previous analysis (data not shown).

Pulmonary Function

Mean FEV₁ before the screening challenge was 3.19 ± 0.17 L. After 7 days of treatment with either zafirlukast or placebo, the prechallenge FEV₁ was significantly higher with zafirlukast than placebo (3.36 ± 0.03 L vs 3.15 ± 0.03 L, $P = 0.001$; Fig 3). After cat exposure, zafirlukast significantly attenuated the decrease in FEV₁ compared with placebo ($-15.1 \pm 2.7\%$ vs $-25.1 \pm 2.7\%$, $P = 0.019$), leading to a significantly greater FEV₁ immediately postchallenge (2.87 ± 0.10 L vs 2.36 ± 0.10 L, $P = 0.002$).

Similar to the results seen with FEV₁, there was greater improvement in PEFR during zafirlukast treatment compared with placebo treatment immediately before allergen-challenge exposure ($P = \text{NS}$), along with a significantly higher PEFR immediately postchallenge (415.4 ± 19.0 L/minute vs 355.6 ± 19.0 L/minute; $P = 0.04$; Fig 4). There was also a significant difference between zafirlukast and placebo in nadir PEFR across the period from end-challenge through 12 hours after challenge (491.1 ± 4.2 L/minute vs 472.2 ± 4.7 L/minute; $P = 0.004$).

Table 1. Screening Demographic Characteristics and Baseline Challenge Responses

Median age (range), years	28.5 (21–49)
Male/female, N	9/9
Median cat wheal (range), mm	10 (5–17)
Median screening FEV ₁ (range), L	3.14 (2.38–4.17)
Median baseline FEV ₁ (range), % predicted value	85 (73–102)
Response to screening challenge	
Median challenge length (range), minutes	20 (10–20)*
Median decrease in FEV ₁ (range), %	23.1 (17.4–56.8)
Median upper airway symptoms score (range)†	5 (2–8)
Median lower airway symptoms score (range)‡	4 (1–6)
Sneeze count	0 (0–3)

FEV₁ = forced expiratory volume in 1 second.

* Duration of exposure was 10 minutes for 6 patients and 20 minutes for 12 patients.

† The maximum possible upper airway symptoms score was 9.

‡ The maximum possible lower airway symptoms score was 6.

No statistically significant difference was observed between zafirlukast and placebo with respect to PEFr-AUC for the 12 hours after the cat challenge (data not shown).

The occurrence of late asthmatic reactions during the study was low, with one placebo-treated patient and three zafirlukast-treated patients demonstrating changes in PEFr between 2 and 12 hours after cat challenge.

Airway Symptoms

Zafirlukast significantly reduced scores for both wheezing ($P = 0.004$) and chest tightness ($P = 0.019$) compared with placebo, and the mean composite lower airway symptom score was decreased by 38% ($P = 0.005$; Table 2). Comparison of symptom scores for the upper airway revealed lower individual and total symptom scores during zafirlukast treatment than during placebo treatment for each measure, but none of the differences between treatments reached statistical significance (Table 2).

Sputum and Nasal Lavage Fluid Cells and ECP

Analysis of induced sputum demonstrated no statistically significant differences between zafirlukast and placebo in total cell counts, cell differential, or ECP (Table 3). Although analysis of nasal lavage fluid revealed significantly fewer total cells and absolute counts of lymphocytes, neutrophils, monocytes, and basophils for zafirlukast compared with placebo, there were no statistically significant differences in absolute or percentage eosinophils or ECP (Table 4).

Safety Results

Adverse events, all of mild or moderate severity, were reported for five patients in the zafirlukast group and four patients in the placebo group. No patient in the zafirlukast group withdrew from therapy because of an adverse event, but one patient in the placebo group withdrew because of pharyngitis. Treatment with zafirlukast was comparable with placebo treatment in terms of safety and tolerability.

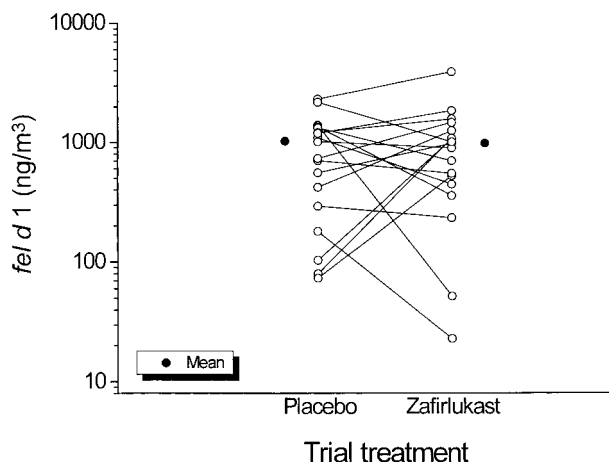


Figure 2. Mean *Fel d 1* concentrations during zafirlukast and placebo challenges.

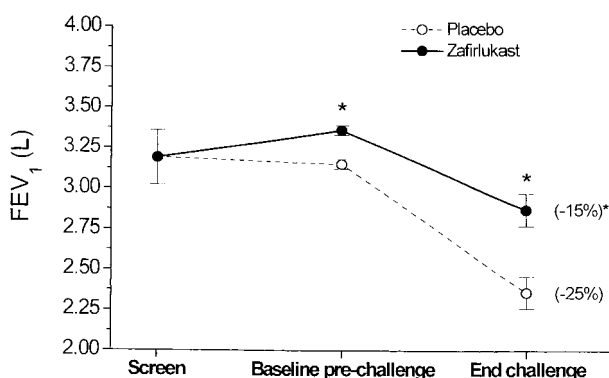


Figure 3. Mean FEV_1 (L) $\pm$ SE for screening challenge, baseline prechallenge, and end-challenge during zafirlukast and placebo treatment. * $P < 0.05$ for zafirlukast versus placebo.

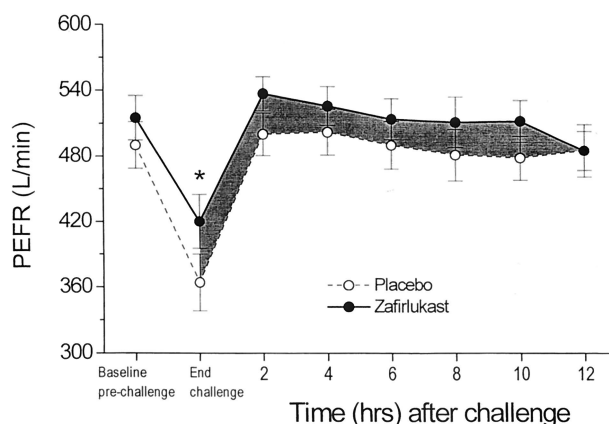


Figure 4. Mean PEFr (L/minute) $\pm$ SE at baseline prechallenge, end-challenge, and hourly measurements for 12 hours postchallenge during zafirlukast and placebo treatment. * $P < 0.05$ for zafirlukast versus placebo for end of challenge PEFr. Shaded area indicates repeated measures analysis of nadir PEFr during the 12 hours postchallenge; $P = 0.004$ for zafirlukast versus placebo. Note: The majority of patients received albuterol at the end of challenge, which may have affected the occurrence of late-phase reactions.

Table 2. Upper and Lower Airway Symptoms Results

Symptom	Zafirlukast mean ($\pm$ SE)	Placebo mean ($\pm$ SE)
Upper airway		
Composite score (0–9)	3.12 (0.29)	3.57 (0.29)
Nasal congestion (0–3)	0.88 (0.12)	1.10 (0.12)
Runny nose (0–3)	1.28 (0.15)	1.40 (0.15)
Nasal itching (0–3)	0.95 (0.14)	1.08 (0.14)
Sneeze (count)	0.77 (0.32)	0.82 (0.32)
Lower airway		
Composite score (0–6)†	2.09 (0.28)	3.39 (0.28)
Chest tightness (0–3)*	1.15 (0.15)	1.71 (0.15)
Wheeze (0–3)†	1.01 (0.14)	1.68 (0.14)

* $P < 0.05$ for zafirlukast versus placebo.† $P < 0.01$ for zafirlukast versus placebo.

DISCUSSION

This study demonstrates that 1 week of treatment with zafirlukast, 20 mg twice daily, significantly improves baseline pulmonary function and attenuates the acute pulmonary response to natural cat allergen exposure. The study did not detect any significant effect on upper airway symptoms, nor was there any significant reduction in either

nasal or sputum eosinophilia or soluble ECP.

Minimally symptomatic subjects who reported nasal and asthmatic symptoms primarily after exposure to cats were selected for the study. The medication requirements for the group reflected this selection bias, as all subjects reported rare use of albuterol unless exposure to cats occurred. Despite

the absence of daily asthma symptoms in these patients, regular use of zafirlukast for 1 week resulted in a significant improvement in baseline FEV₁ (5% above baseline). This finding provides additional confirmation that regular therapy with a maintenance medication may benefit patients with even very mild asthma.

The significant protective effect of zafirlukast on the immediate pulmonary response to cat exposure strongly mirrors what has been shown in previous studies using both nebulized provocation^{5,7–8} and cat room challenge.⁹ In addition to producing these effects on the early asthmatic response, zafirlukast and other leukotriene D₄ receptor antagonists also attenuate the late asthmatic response to nebulized allergen.^{5,7–8} The rate of late asthmatic reactions was very low in our study (1 in 18 during placebo treatment and 3 in 17 during zafirlukast treatment). This 6% incidence of late reactions during placebo treatment contrasts with an incidence of 50% or more

Table 3. Sputum Induction Results

	Zafirlukast		Placebo	
	Prechallenge mean ($\pm$ SE)	Postchallenge mean ($\pm$ SE)	Prechallenge mean ($\pm$ SE)	Postchallenge mean ($\pm$ SE)
Total cells, 10 ⁴ cells/mm ³	671.8 (128.9)	931.3 (247.0)	656.7 (124.6)	554.2 (118.0)
Lymphocytes, 10 ⁴ cells/mm ³	58.3 (11.9)	141.1 (42.8)	59.1 (12.3)	72.5 (16.8)
Basophils, 10 ⁴ cells/mm ³	10.6 (2.3)	35.9 (13.0)	9.4 (2.7)	17.49 (5.2)
Neutrophils, 10 ⁴ cells/mm ³	187.1 (32.5)	212.9 (48.7)	210.7 (41.2)	135.4 (26.4)
Eosinophils, 10 ⁴ cells/mm ³	11.8 (3.8)	76.1 (25.8)	14.8 (3.1)	31.5 (8.3)
Eosinophils, %	2.1 (0.4)	6.5 (0.8)	2.6 (0.4)	5.5 (0.7)
ECP, ng/mL	73.7 (5.1)	298.1 (39.4)	74.1 (4.9)	251.3 (38.0)

ECP = eosinophil cationic protein.

Table 4. Nasal Lavage Results

	Zafirlukast		Placebo	
	Prechallenge mean ($\pm$ SE)	Postchallenge mean ($\pm$ SE)	Prechallenge mean ($\pm$ SE)	Postchallenge mean ($\pm$ SE)
Total cells, 10 ⁴ cells/mm ³ *	65.5 (34.4)	43.3 (23.3)	25.6 (7.7)	44.8 (9.4)
Lymphocytes, 10 ⁴ cells/mm ³ *	8.6 (4.6)	9.7 (6.3)	3.1 (0.8)	7.6 (1.6)
Basophils, 10 ⁴ cells/mm ³ *	1.6 (0.9)	1.6 (0.7)	0.9 (0.3)	1.9 (0.5)
Neutrophils, 10 ⁴ cells/mm ³ *	32.5 (16.7)	12.3 (4.8)	13.5 (4.1)	17.5 (3.6)
Eosinophils, 10 ⁴ cells/mm ³	2.8 (1.8)	4.5 (2.9)	1.3 (0.6)	3.1 (0.8)
Eosinophils, %	3.4 (0.5)	8.4 (1.0)	3.2 (0.6)	6.3 (0.7)
ECP, ng/mL	2.8 (0.2)	12.9 (1.5)	3.1 (0.3)	9.7 (1.1)

ECP = eosinophil cationic protein.

* $P < 0.05$ for zafirlukast versus placebo. Analysis of covariance based on ranked data using day 6 prechallenge data as baseline.

in most previous studies in which allergen was delivered by nebulizer.¹⁴ One reason for the low incidence noted in our study may have been the use of albuterol immediately after the cat challenge in most of the subjects, although others have determined that use of an inhaled short-acting β -adrenergic agonist before allergen challenge does not prevent the occurrence of late-phase responses.¹⁵ It is also possible that we may have missed the occurrence of late responses by relying on PEFr instead of spirometry. However, a recent study of 11 patients failed to detect any late asthmatic reactions after cat room challenge despite using spirometry to evaluate pulmonary function.¹⁶ These results suggest that natural exposure to cat allergen may be markedly less likely to induce late asthmatic reactions than is challenge by nebulizer. The reasons for the differences seen between nebulized versus natural allergen delivery are uncertain, but may be related to the size and deposition of respirable allergenic particles, as well as other factors not yet identified.

Sulfidopeptide leukotrienes released during allergic reactions have a number of important effects upon the lower airways, including bronchoconstriction, mucus secretion, and airway edema.¹⁷ In addition, these mediators seem to act as significant cofactors in attracting eosinophils into the airways of asthmatic patients.^{18–20} In the present study, zafirlukast did not inhibit the number or percentage of sputum eosinophils after cat exposure. Similar findings have been noted with leukotriene (LTD_4) antagonists using other methods of allergen challenge. Calhoun et al¹⁰ demonstrated that zafirlukast, 20 mg twice daily, significantly reduced the number of lymphocytes and basophils, but not eosinophils, in BAL fluid after segmental allergen challenge. Montelukast, 10 mg once daily, also failed to prevent increases in sputum eosinophilia after nebulized allergen challenge.²¹ Calhoun et al²² also demonstrated, however, that a larger dose of zafirlukast (160 mg twice daily) caused a significant reduction in BAL fluid eosinophilia. These studies document that

LTD_4 antagonists, given in approved doses, do not affect airway eosinophilia after a single allergen exposure. In contrast to the acute effects of these drugs, one study demonstrated that long-term use of montelukast attenuated sputum eosinophilia in chronic asthma.²³ Further evidence regarding the anti-inflammatory effects of LTD_4 antagonists in chronic asthma is awaited before definitive conclusions can be drawn.

Leukotrienes have been implicated in the pathophysiology of allergic rhinitis. A study by Creticos et al²⁴ demonstrated the release of LTC_4 after nasal allergen provocation. In addition, previous studies with zafirlukast, zileuton, and montelukast have demonstrated small but statistically significant reductions in the nasal response to acute allergen exposure.^{9,11,25} Chronic dosing trials in patients with seasonal allergic rhinitis demonstrated a significant reduction in one study²⁶ but not in another study.²⁷ In the latter study, there were also no detectable differences in nasal pathology comparing placebo and the leukotriene inhibitor after seasonal allergen exposure.²⁷ Our results demonstrate that nasal symptoms were slightly reduced after treatment with zafirlukast, but these changes did not reach statistical significance. In contrast to the moderate to severe pulmonary responses noted in this study, the overall intensity of nasal allergic reactions was quite mild, with the mean composite score of 3.57 (on a 9-point scale) and a mean sneeze count of <1. It is possible that the minor nasal response elicited by cat challenge may not have been sufficient to detect any treatment effect with zafirlukast.

CONCLUSION

This study demonstrates the effectiveness of zafirlukast in reducing the acute pulmonary response to natural cat allergen exposure, but it failed to document significant effects of the drug on nasal symptoms or anti-inflammatory effects in the lower airways.

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Requests for reprints should be addressed to:
Jonathan Corren, MD
Allergy Research Foundation, Inc
11620 Wilshire Blvd, Suite 200
Los Angeles, CA 90025
E-mail: joncorren@hotmail.com