

The effect of zafirlukast on repetitive exercise-induced bronchoconstriction: The possible role of leukotrienes in exercise-induced refractoriness

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Background: Single doses of zafirlukast attenuate exercise-induced bronchoconstriction (EIB), but previous studies have not measured zafirlukast's effects after regular dosing or its duration of effect beyond 4 hours.

Objective: The purpose of this study was to assess the effects of zafirlukast 20 mg and 80 mg twice daily compared with placebo on exercise challenges performed at 2 and 8 hours after the last dose of regular administration.

Methods: Twenty-four adult patients with stable asthma taking β_2 -agonists, inhaled corticosteroids, or both received treatment with zafirlukast (20 mg and 80 mg) and placebo. The patients were treated twice daily for 14 days in a randomized, double-blind, 3-way cross-over fashion, with a 7-day washout period between each treatment. Exercise challenges were performed at 2 and 8 hours after the morning dose on day 14. FEV₁ was measured before exercise and at set intervals after exercise until it returned to within 7% of its baseline value.

Results: Both zafirlukast treatments significantly reduced EIB, as measured by the area under the FEV₁ time curve after the 2-hour ($P < .001$) and 8-hour ($P < .001$) exercise challenges and maximum fall in FEV₁ at the 2-hour challenge ($P < .001$). The comparison at 8 hours between treatments was affected by the unexpected finding that EIB was less in the placebo group after the 8-hour challenge than after the 2-hour challenge, as measured by the within-group change in the maximum fall in FEV₁ ($P < .001$) and the area under the FEV₁ time curve ($P = .0023$).

Conclusion: Regular zafirlukast treatment protects against EIB for at least 8 hours after regular dosing. A refractory period, which may be caused by exercise-induced leukotriene release, may last for up to 6 hours after the initial response to exercise. (*J Allergy Clin Immunol* 1999;1155-61.)

Key words: Exercise-induced asthma, exercise-induced refractoriness, leukotriene-receptor antagonists, zafirlukast

Abbreviations used

EIB: Exercise-induced bronchoconstriction

FEV₁-AUC₁₋₃₀: Area under the FEV₁ time curve

In clinical practice 75% of patients with asthma experience bronchoconstriction after exercise,¹ a condition known as exercise-induced bronchoconstriction (EIB). Several hypotheses have been postulated to explain the mechanism of this bronchoconstriction. These include cooling and dehydration of the fluid lining of the airways leading to rebound vasodilatation after exercise,²⁻⁴ release of inflammatory mediators from mast cells and lung tissue,⁵ or both, as the bronchi attempt to normalize the condition of the inspired air to body temperature.⁶ These mediators include the cysteinyl leukotrienes that induce constriction of bronchial smooth muscle, airway edema, and hypersecretion of mucus.⁷ Evidence for the role of leukotrienes in the etiology of EIB is based on an increase in urinary leukotriene E₄ after exercise in patients with asthma⁸ and the attenuation of EIB by cysteinyl leukotriene-receptor antagonists⁹⁻¹² and a leukotriene-synthesis inhibitor.¹³ In some subjects with EIB, exercise under laboratory-controlled conditions is followed by a refractory period, during which exercise of the same intensity produces less bronchoconstriction.^{14,15} In a previous study in children with asthma, the refractory period after an initial exercise challenge extended for a period of less than 4 hours.¹⁶

Zafirlukast is a competitive and selective leukotriene-receptor antagonist¹⁷ that has been shown to attenuate EIB when taken as a single dose up to 4 hours before exercise.^{9,18,19} The purpose of this study was to assess the effects of zafirlukast 20 mg and 80 mg twice daily compared with placebo on exercise challenges performed at 2 and 8 hours after the final morning dose after 14 days of regular treatment.

METHODS

Subjects

Subjects were screened for participation at 4 centers in France (Lille, Montpellier, Paris, and Pessac). All the subjects recruited were nonsmoking patients with stable asthma (ie, no change to asthma medication in the month before screening), aged 18 to 45

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years, with an FEV₁ of 75% or greater of the predicted value at screening. Their treatment included short-acting β_2 -agonists with or without inhaled corticosteroids at a daily dose of up to 1000 μ g (beclomethasone dipropionate, or budesonide). Pregnant or lactating females were considered ineligible. Subjects were also excluded if they had required oral corticosteroids or been hospitalized because of asthma in the 3 months before screening or if they had an upper or lower respiratory tract infection within 6 weeks before screening. Subjects treated with long-acting β_2 -agonists, cromolyn sodium, or nedocromil sodium 2 weeks before screening or theophylline 1 week before screening were also excluded from the study. Existing treatment with inhaled corticosteroids remained constant during the study, and aerosol and dry-powder formulations of short-acting β_2 -agonists were permissible for the relief of symptoms. The study was conducted according to the precepts of good clinical practice. An ethics committee from each participating center approved the study protocol and each patient provided written informed consent before agreeing to participate in the study.

Study design

Subjects with a postexercise fall in FEV₁ greater than 15% from the pre-exercise (baseline) value during the 1-week screening period were randomized to the double-blind, 3-way cross-over period, in which they received placebo, zafirlukast 20 mg, and zafirlukast 80 mg twice daily for 14 days in random sequence. There was a 7-day washout period between each of the 3 treatment periods.

Exercise challenge

Standard exercise challenges were conducted during the screening period to establish whether the subject met the entry criteria and at 2 and 8 hours after the morning dose on the last day (day 14) of each treatment period. Baseline FEV₁ was recorded before the subject exercised on a bicycle ergometer while inspiring dry air at room temperature. The initial workload for the screening exercise challenge was chosen according to the patient's physical fitness. The workload was rapidly increased over 2 to 3 minutes until the target heart rate (defined as $0.8 \times [220 - \text{the subject's age in years}]$) was reached, and exercise was then continued for an additional 6 minutes. FEV₁ was measured 1, 5, 10, 15, and 30 minutes after exercise had terminated and then every 10 minutes until the FEV₁ returned to within 7% of its baseline value. Pre-exercise FEV₁ was recorded as the highest of 3 consecutive maneuvers. To avoid close succession of repeated forced expiratory maneuvers that might in itself affect bronchial tone and therefore bias the results, a single well-controlled maneuver was deemed adequate to record postexercise FEV₁ at each time point. Baseline FEV₁ was defined as the higher of the pre-exercise or 1-minute postexercise FEV₁ values. Pulse rate was measured before exercise commenced and continuously throughout exercise by using an oscilloscope attached to a precordial electrocardiographic lead. The same conditions and workload established during screening were used for all subsequent challenges for that patient. Subjects were permitted to use albuterol, terbutaline, or fenoterol administered by means of metered-dose inhaler or dry-powder formulations for symptomatic relief. For those whose treatment included inhaled corticosteroids at entry, the dose of inhaled corticosteroids remained unaltered throughout the study period. Subjects were not permitted to take inhaled β_2 -agonists, inhaled corticosteroids, or antihistamines for at least 6, 12, and 24 hours, respectively, before any exercise challenge.

Data analysis

The maximum fall in FEV₁ was the lowest FEV₁ recorded after exercise expressed as a percentage of baseline FEV₁. The area under the FEV₁ time curve (FEV₁-AUC₁₋₃₀) was calculated from

the percentage change from baseline FEV₁ over the 30-minute observation period by using the trapezoidal method. If the 30-minute data point was missing (or invalid because of the use of rescue medication) and if no data points were available after 30 minutes, the percentage change at this time point was estimated by using a straight-line extrapolation from the 2 previous data points. If there were later time points, the 30-minute data point was obtained by interpolation.

ANOVA models were fitted to the 2-hour and 8-hour exercise challenges for the maximum percentage fall in FEV₁ and FEV₁-AUC₁₋₃₀ and included between-patient effects of treatment sequence and patient-within-treatment sequence and the within-patient effects of period and treatment. Treatment effects were estimated separately for each dose of zafirlukast versus placebo. Ordinary least-squares mean treatment differences were calculated, together with their associated 95% confidence intervals and *P* values. In addition, the percentage of protection of active treatment over placebo was estimated as 100 times the ratio of the least-squares mean treatment difference to the least-squares mean effect of placebo.

For each of the 3 treatments, a post hoc, 2-sided, paired *t* test was used to compare the results from the 2- and 8-hour time points, with respect to the maximum fall in FEV₁ and FEV₁-AUC₁₋₃₀, for those subjects who provided data at both time points.

Safety

The investigator recorded adverse events reported by the patient during the study on a case record form. Venous blood samples were taken for routine hematology and clinical chemistry at the screening visit and before and at the end of each treatment period. Twelve-lead electrocardiograms were recorded at screening and at the end of each of the 3 treatment periods.

RESULTS

Of the 30 subjects who were initially screened for participation in the study, 24 were randomized to treatment (Table I). The mean (SD) age was 23 (7) years, and the mean (SD) duration of asthma was 13 (9) years. All subjects were being treated with inhaled β_2 -agonists as needed, and all but 6 subjects were corticosteroid-naïve patients. The 6 subjects who received inhaled corticosteroids (800-1000 μ g/d) had, on average, less severe EIB than those who did not. The general pattern of results was, however, consistent across the 2 groups, with the protective effect of zafirlukast on EIB being similar in subjects with and without inhaled corticosteroids. Twenty-three of the 24 subjects were nonsmokers, and one was an exsmoker. A positive response (ie, wheal dermal reaction with diameter >3 mm) to a skin prick test was observed in 13 subjects. Subject 1 was withdrawn from the study after an urticarial-type rash developed on the last day of his placebo treatment period; 23 patients completed the study. Protocol deviations in 7 subjects resulted in some data being excluded from 1 or more analyses. These deviations included the following: changes in exercise workload from the workload established at the screening visit (5 subjects), a 2-hour challenge conducted less than 1 hour or more than 3 hours after the last dose of study drug or an 8-hour challenge conducted less than 7 and more than 9 hours after the last dose (3 subjects), exercise challenge conducted

TABLE I. Prestudy characteristics of subjects randomized to treatment

Patient	Age (y)	Sex	FEV ₁ [*]	Response to exercise [†]	Asthma medication	Atopy [‡]
1	19	M	84.0	68.5	Sal-prn	Yes
2	22	M	94.0	22.5	Terb-prn	Yes
3	21	M	103.5	24.0	Sal-prn	No
4	26	M	88.5	41.0	Sal-prn	Yes
5	33	M	83.0	37.5	Sal-prn	No
6	19	F	81.0	17.5	Sal-prn	No
7	22	M	101.0	17.5	Sal-prn	No
8	23	M	92.5	41.0	Sal-prn	Yes
9	21	M	89.0	22.5	Sal-prn	Yes
10	18	F	100.5	16.5	Sal-prn	No
11	27	M	100.0	59.5	Sal-prn	Yes
12	18	M	99.0	33.0	Sal-prn	Yes
13	18	M	108.0	15.0	Sal-prn	No
14	22	F	115.0	47.0	Sal-prn	Yes
15	20	F	96.0	23.0	Sal-prn	No
16	26	F	102.5	28.0	Sal-prn	No
17	21	F	81.0	25.5	Sal-prn	No
18	18	M	97.5	18.5	Sal-prn	No
19	22	F	112.0	14.5	Sal-prn/BDP-1000	Yes
20	23	F	81.0	12.5	Sal-prn/BDP-1000	Yes
21	22	M	100.0	26.5	Sal-prn/BDP-1000	No
22	18	M	99.0	17.0	Sal-prn/BDP-1000	Yes
23	36	M	104.5	17.0	Sal-prn/BUD-1000	Yes
24	45	M	89.5	16.5	Terb-prn/BUD-800	Yes
Mean ± SD	23.3 ± 6.5		95.7 ± 9.8	26.2 ± 13.1		

Sal, Salbutamol; Terb, terbutaline; Prn, as required; BDP, beclomethasone dipropionate; BUD, budesonide; 800 or 1000, constant dose of corticosteroid (micrograms per day) used by the patient throughout the study.

*FEV₁ is expressed as the percentage of predicted normal value.

[†]Maximum percentage fall in FEV₁ from the pre-exercise baseline at screening.

[‡]Response to a dermal challenge of an allergen known to precipitate asthma.

within 6 hours of administration of β_2 -agonists (2 subjects), and less than 85% compliance with study treatment (2 subjects).

Both doses of zafirlukast reduced the postexercise fall in FEV₁ and FEV₁-AUC₁₋₃₀ (Table II and Fig 1). Compared with placebo, zafirlukast 20 mg and 80 mg twice daily reduced the maximum postexercise fall in FEV₁ by 35% ($P < .001$) and 49% ($P < .001$), respectively, after the 2-hour exercise challenge and by 23% ($P = .18$) and 27% ($P = .13$), respectively, after the 8-hour exercise challenge. Compared with placebo, zafirlukast 20 mg and 80 mg twice daily also reduced the postexercise fall in FEV₁-AUC₁₋₃₀ by 60% ($P < .001$) and 70% ($P < .001$), respectively, after the 2-hour exercise challenge and by 45% ($P = .001$) and 56% ($P < .001$), respectively, after the 8-hour exercise challenge.

After treatment with placebo, the response to the exercise challenge 8 hours after the last dose was significantly less than the response 2 hours after the last dose. This lesser response to repeat exercise, which was not observed with either dose of zafirlukast treatment, was significant for both the maximum fall in FEV₁ ($P < .001$) and FEV₁-AUC₁₋₃₀ ($P = .0023$). Compared with the maximum fall in FEV₁ after the 2-hour exercise challenge, the maximum fall in FEV₁ after the 8-hour exercise challenge was smaller in all 17 of the subjects receiving

placebo (Fig 2). In comparison, the maximum fall in FEV₁ was less after the second challenge in only 10 of the 17 and 11 of the 18 subjects after treatment with zafirlukast 20 mg and 80 mg, respectively (Table III).

All the analyses were also performed in an intention-to-treat population (including all deviations from protocol). The results were similar to, and entirely consistent with, the per protocol analyses.

The incidence of adverse events reported during the study was similar for the 3 treatment groups. Seven patients reported 11 adverse events while receiving zafirlukast 80 mg twice daily, 2 patients reported 5 adverse events while receiving zafirlukast 20 mg twice daily, and 5 patients reported 10 adverse events while receiving placebo. The most frequently reported adverse events were worsening of allergic rhinitis (1 subject in each treatment group) and pharyngitis (1 subject in the placebo group and 2 subjects in the zafirlukast 80 mg group). There were no clinically significant changes with respect to hematology, clinical chemistry, or echocardiographic traces recorded during the study. Only 1 patient was withdrawn from the study because of an adverse event. This patient was randomized to receive treatment first with zafirlukast 20 mg followed by placebo. On the last day of the placebo period, urticaria developed in this patient, which lasted for 2 days and led to his withdraw-

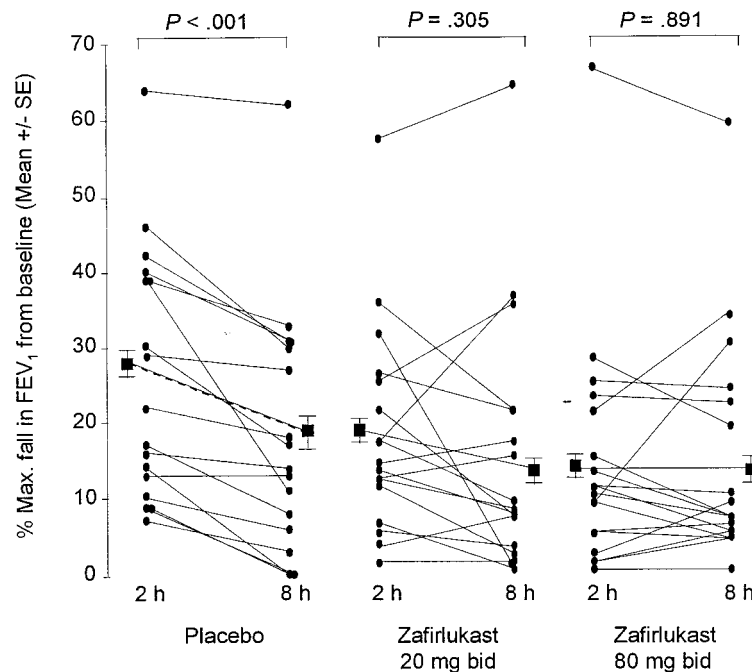


FIG 1. Mean (SEM) percentage change in baseline FEV₁ after a controlled exercise challenge at 2 and 8 hours after the final morning dose of study drug. Each treatment period consisted of 14 days of randomized treatment with either placebo (**A**), zafirlukast 20 mg twice daily (*bid*; **B**), or zafirlukast 80 mg twice daily (**C**). The nonshaded area represents mean falls in FEV₁ from baseline of at least 15%; this represents the minimum level defined during screening for eligibility to enter the study.

TABLE II. Comparison of the effect of twice daily zafirlukast 20 mg and 80 mg with placebo on the postexercise maximum percentage of change in FEV₁ and FEV₁-AUC₁₋₃₀ for exercise challenges conducted 2 and 8 hours after treatment

Time of exercise challenge	Comparison vs placebo	Least-squares mean difference between active treatment and placebo (95% CI)	P value	Protection* (%)
Maximum change in FEV ₁ (%)				
2 h	Zafirlukast 80 mg	-13.3 (-18.2, -8.5)	<.001	48.7
	Zafirlukast 20 mg	-9.6 (-14.2, -4.9)	<.001	34.9
8 h	Zafirlukast 80 mg	-4.8 (-11.1, 1.4)	.125	27.1
	Zafirlukast 20 mg	-4.1 (-10.3, 2.1)	.183	23.2
FEV ₁ -AUC ₁₋₃₀ (% min)				
2 h	Zafirlukast 80 mg	455 (322, 588)	<.001	70.4
	Zafirlukast 20 mg	391 (258, 524)	<.001	60.4
8 h	Zafirlukast 80 mg	279 (153, 405)	<.001	56.0
	Zafirlukast 20 mg	225 (97, 352)	<.001	45.1

CI, Confidence interval.

*Protection = [least-squares mean placebo - least-squares mean active/least-squares mean placebo] × 100.

al from the study. The urticaria was successfully treated with oral steroids and antihistamines, and the investigator did not consider this adverse event to be related to study treatment.

DISCUSSION

Zafirlukast is a competitive antagonist of the cysteinyl leukotrienes that improves pulmonary function, reduces the incidence and severity of asthma symptoms, and

reduces the need for inhaled β_2 -agonists in mild-to-moderate asthma.²⁰ The profile of its effect on EIB, however, is incomplete. In adults a single dose of zafirlukast given either orally⁹ or by inhalation¹⁸ up to 2 hours before controlled exercise challenge has been shown to inhibit EIB by more than 50% and to greatly shorten the time to recovery of normal lung function. In children, single doses of zafirlukast 5 mg, 20 mg, and 40 mg taken 4 hours before controlled exercise challenge attenuate EIB by more than 50%.¹⁹ In our study in adult patients with

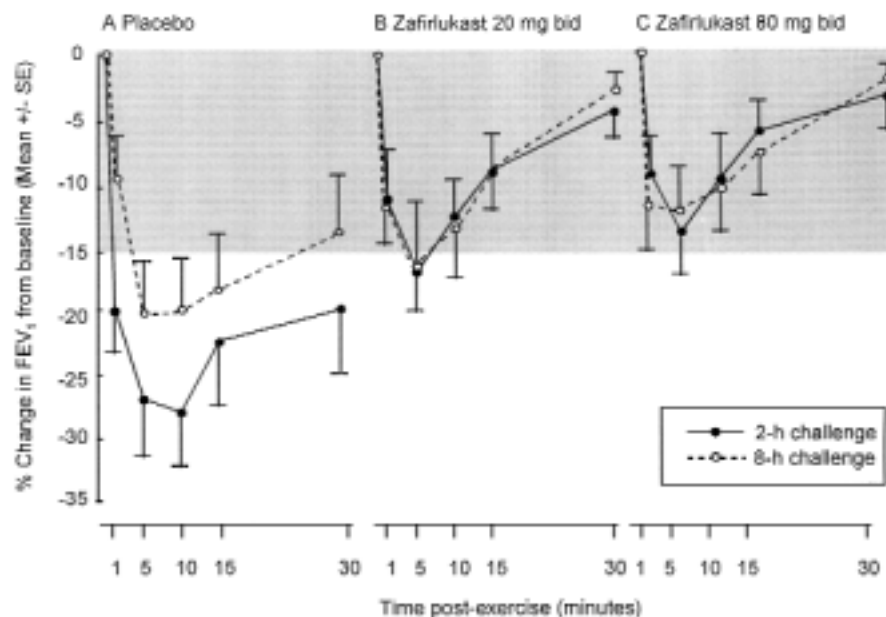


FIG 2. Maximum fall in FEV₁ between the first and second exercise challenge performed 2 and 8 hours after the final morning dose of test treatment in individual patients. Challenge days followed 14 days of randomized treatment with either placebo, zafirlukast 20 mg twice daily (*bid*), or zafirlukast 80 mg *bid*.

TABLE III. Effect of repeat exercise provocation at 2 and 8 hours after dosing during each of the 3 treatment periods

Treatment period	n	Mean (SEM) % difference between 2-h and 8-h EIB	% Range	P value
Maximum change in FEV ₁ (%)				
Placebo	17	-8.3 (1.7)	-27.5 to -0.2	<.001
Zafirlukast 20 mg	17	-2.9 (2.7)	-31.1 to 19.8	.305
Zafirlukast 80 mg	18	0.3 (1.8)	-8.4 to 20.8	.891
FEV ₁ -AUC ₁₋₃₀ (% min)				
Placebo	12	-155 (39)	-482 to 12	.002
Zafirlukast 20 mg	13	-17 (50)	-238 to 421	.740
Zafirlukast 80 mg	14	3 (42)	-214 to 370	.937

Comparisons were made by using both the maximum percentage change in FEV₁ and FEV₁-AUC₁₋₃₀. Negative values indicate a smaller response to exercise at the 8-hour challenge compared with the earlier 2-hour challenge.

n, Number of repeat challenges available for comparison at both time points (data have been excluded where rescue bronchodilator was used).

asthma, similar levels of protection have been seen with zafirlukast 20 mg and 80 mg twice daily 2 and 8 hours after administration of a final morning dose.

The comparison with placebo for the 8-hour exercise challenge results was affected by the unexpected finding that when patients received placebo, both the maximum fall in FEV₁ and the FEV₁-AUC₁₋₃₀ were significantly less after the 8-hour exercise challenge than they were after the 2-hour exercise challenge. Despite a considerable heterogeneity in response to exercise, this apparent refractoriness to further exercise after placebo treatment was consistent in that the fall in FEV₁ occurred in all subjects with 2 placebo challenges, and the fall in FEV₁-AUC₁₋₃₀ occurred in all but 1 subject with 2 placebo challenges. Previous studies have demonstrated that when exercise challenges were repeated at intervals of 2 hours or less, a lesser degree of bronchoconstriction after the second exercise challenge was observed in some

patients.^{14,15} This finding led to an investigation of the time course to recovery after a bronchoconstrictive challenge.¹⁶ In this study, performed in 9 asthmatic children 9 to 14 years of age, recovery from full bronchoconstriction after exercise challenge took place within 4 hours. Studies involving repeat exercise challenges more than 4 hours apart in adult patients with asthma have reported conflicting results. In a large study in 161 adults comparing salmeterol and albuterol, a trend for a reduction in the area under the percentage of predicted FEV₁ time curve followed repeat exercise challenges, but no significant difference was seen between the maximum falls in FEV₁ between each of the challenges.²¹ By contrast, Bronsky et al¹² reported a 25% reduction in the placebo EIB after a repeat challenge 10 to 12 hours after the initial challenge, which was not reported after administration of the leukotriene-receptor antagonist montelukast. Because this was outside the known refractory period for

exercise, this observation was unexplained. These results may suggest that the refractory period in adult subjects with asthma may last for longer than 4 hours. Further prospective studies are needed to confirm this.

Circadian variations in response of the airways to exercise might account for the reduced placebo EIB to repeat challenge in our study and in the study performed by Bronsky et al.¹² However, this hypothesis does not readily explain why refractoriness occurred only after placebo treatment in both studies and not during treatment with the leukotriene-receptor antagonists. One hypothesis, suggested by Manning et al,²² for the development of refractoriness is that inhibitory PGs, either PGE₂ or prostacyclin, are released during the initial exercise provocation and that these PGs then partially protect the airways against further EIB. The trigger for the release of these putative inhibitory PGs is unknown, but it is likely that it is mediated by leukotriene release during the initial exercise challenge. This hypothesis is supported by the results of studies that demonstrated that tachyphylaxis occurs on repeat leukotriene D₄ challenge and that cross-tachyphylaxis between exercise challenge and leukotriene D₄ challenge can also occur, but both are attenuated by pretreatment with a cyclooxygenase inhibitor. Consistent with this hypothesis is the demonstration of attenuation of EIB after exogenous administration of PGE₂.²³ In our study we did not observe refractoriness after zafirlukast treatment, presumably because occupancy of the cysteinyl leukotriene receptor prevented the leukotriene-mediated release of inhibitory PGs during the initial exercise challenge.

In clinical practice, inhaled β_2 -agonists and inhaled cromolyn sodium are taken shortly before exercise to prevent EIB in patients with asthma. Long-acting β_2 -agonists have the convenience of twice daily administration, but their protective effect against EIB diminishes with regular administration.^{24,25} There is therefore a clinical need for a drug that provides long-acting protection with no diminution of effect with repeat dosing. There are currently 2 leukotriene-receptor antagonists (zafirlukast and montelukast) that may fulfill this need. Bronsky et al¹² studied montelukast at a range of doses (0.4, 2, 10, and 50 mg once daily) and demonstrated a modest protection against exercise challenge that was of statistical significance and dose related at 20 to 24 hours, with no effect at 32 to 36 hours after treatment. No tachyphylaxis to this level of protection at 20 to 24 hours was reported in a further study of 12 weeks' duration.²⁶ Whether greater levels of protection against EIB are afforded by montelukast at times less than 20 hours after treatment remains to be established. Regular twice daily dosing with zafirlukast in our study attenuated EIB for at least 8 hours after a final morning dose, with no change in the profile of the EIB compared with the 2-hour response, with both doses of zafirlukast. Further studies are necessary to establish whether the attenuation of EIB by zafirlukast in this study persists for longer than 8 hours after regular dosing and whether this protective effect is maintained over longer treatment periods.

In conclusion, zafirlukast is an important addition to current antiasthma therapies for the prevention of exercise-induced symptoms. The results of this study may also have implications for the design of future studies that involve repeated exercise challenges or other indirect challenges, which may involve the release of leukotrienes.

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