

Onset and duration of protection against exercise-induced bronchoconstriction by a single oral dose of montelukast

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Background: Leukotriene modifiers have been shown to protect against exercise-induced bronchoconstriction (EIB) with repeated, chronic dosing.

Objective: To study the onset and duration of protection against EIB after a single dose of montelukast, a leukotriene receptor antagonist.

Methods: In this randomized, crossover, double-blind study, 51 adult asthma patients with EIB ($\geq 20\%$ postexercise decrease in forced expiratory volume in 1 second [FEV₁]) received a single oral dose of montelukast (10 mg), or placebo followed by exercise challenge 2, 12, and 24 hours after dosing. The primary end point was maximum percentage decrease in FEV₁ from preexercise baseline during 60 minutes after the 2-hour challenge.

Results: At 2, 12, and 24 hours after dosing, the maximum decrease in FEV₁ was $10.8\% \pm 7.9\%$, $8.4\% \pm 7.5\%$, and $8.3\% \pm 7.3\%$ for montelukast and $22.3\% \pm 13.1\%$, $16.1\% \pm 10.2\%$, and $16.9\% \pm 11.7\%$ for placebo, respectively ($P \leq .001$ at each time point). Postexercise recovery was quicker with montelukast than with placebo ($P \leq .001$); mean (95% confidence interval) differences were -26.8 minutes (-35.1 to -18.4 minutes), -16.0 minutes (-22.9 to -9.2 minutes), and -17.4 minutes (-24.9 to -9.9 minutes) at the 3 time points, respectively. At all time points, area under the curve for percentage decrease in FEV₁ during 60 minutes after exercise was smaller after montelukast ($P \leq .001$); montelukast protected more patients against EIB ($P \leq .001$). Fewer patients required postexercise β -agonist rescue at 2 hours after dosing with montelukast ($P = .03$).

Conclusion: Montelukast provided significant protection against EIB as soon as 2 hours after a single oral dose, with persistent benefit up to 24 hours.

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INTRODUCTION

Exercise-induced bronchoconstriction (EIB), also known as exercise-induced asthma, is a common clinical manifestation of asthma and occurs in up to 80% to 90% of asthmatic patients.¹ EIB is associated with inflammatory cell release of mediators such as histamine and cysteinyl leukotrienes that are potent bronchoconstrictors.^{2,3} Urinary excretion of leukotriene E₄ increases after exercise challenge in asthmatic patients,^{4,5} and several lines of evidence support an important role for the leukotrienes in the pathogenesis of EIB.^{6,7}

Treatment with leukotriene modifiers attenuates EIB.^{8–13} Montelukast, a cysteinyl leukotriene receptor antagonist, is an anti-inflammatory agent with bronchodilator activity that has shown clinical benefit in asthmatic patients 1 year and older.^{14–16} Montelukast has been shown to be effective in attenuating EIB in adults and children.^{17–19}

Data on the onset and duration of action of prophylactic treatments against EIB are important for choosing appropriate therapies for patients. Cromolyn, nedocromil, and albuterol provide no more than a few hours of protection, necessitating repetitive inhalational dosing.²⁰ Newer agents, including inhaled long-acting β_2 -agonists (salmeterol, formoterol) and oral leukotriene modifiers, have longer durations for the prevention of EIB.^{8,21} Nevertheless, data describing efficacy during 24 hours after a single dose are limited. For instance, although montelukast has usually been evaluated for EIB at the end of a 24-hour dosing interval in repeated-dosing studies, much remains to be understood about the early time course and extent of its protection against EIB after a single dose. Leukotriene receptor antagonists are known to produce bronchodilation within minutes of intravenous administration.^{22,23} Oral montelukast is absorbed quickly, with a time to peak plasma concentration of 3 to 4 hours in adults.²⁴ For this reason, we measured the onset of effect of a single dose of montelukast for protection against EIB as early as 2 hours after dosing, and the duration of effect was measured at 12 and 24 hours after dosing.

METHODS

Study Design and Patients

Protocol 270 was a randomized, double-blind study conducted between July and November 2003 at 9 centers. Fol-

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lowing 2 prestudy visits, eligible patients were randomized using a computer-generated schedule to 1 of 2 treatment sequences. Patients in sequence 1 received a single oral dose of montelukast (10 mg) in the morning, followed by a wash-out interval of 3 to 7 days, then crossed over to matching placebo; patients in sequence 2 received placebo and montelukast in the reverse order. After each treatment, patients underwent exercise challenge 2, 12, and 24 hours after dosing; challenges were consistently performed in the morning, early evening, and the following morning. Patients ran for 6 minutes on a treadmill to increase heart rate to 80% to 90% of the predicted maximal heart rate for age. Forced expiratory volume in 1 second (FEV_1) measurements were made 5 minutes before dosing, 5 minutes before exercise, and 0, 5, 10, 15, 30, 45, and 60 minutes after ending the exercise challenge. Across the time points from 0 to 60 minutes after exercise, the lowest FEV_1 was selected to identify the maximum decrease in FEV_1 at that challenge for that patient (Fig 1).

Patients (15–45 years of age) had mild-to-moderate stable asthma, with a preexercise, prebronchodilator FEV_1 of 70% or higher of predicted and a maximal decrease in FEV_1 of 20% or higher (from the preexercise FEV_1 measured 5 minutes before each challenge) after exercise challenge at each of the 2 prestudy visits. Patients with severe EIB (defined as a maximum percentage decrease in FEV_1 of $>40\%$) and those with asthma exacerbations during the 5 weeks before randomization were excluded from the study. Patients taking asthma medications, other than those taking a stable dose of inhaled corticosteroids for at least 4 weeks before the first prestudy visit, were not eligible to participate. Use of an inhaled short-acting β -agonist within 8 hours before an exercise challenge was not permitted; however, such rescue medication was allowed as needed after an exercise challenge and otherwise throughout the study. 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 prespecified primary end point was the maximum percentage decrease in FEV_1 after exercise challenge (Fig 1) at 2 hours after dosing. Secondary end points (Fig 1) included maximum percentage decrease in FEV_1 at 12 and 24 hours after dosing and the following end points (measured after each challenge): time to recovery of FEV_1 to within 5% of preexercise baseline, area under the curve for percentage decrease in FEV_1 during 60 minutes after exercise ($AUC_{0-60\text{ min}}$), and the number of patients who required β -agonist rescue within 90 minutes after exercise.

Statistical Analysis

The intention-to-treat approach for efficacy analyses included all patients with at least one efficacy measurement on both treatments of the sequence. Data are presented as least squares means and 95% confidence intervals (CIs). Analyses for maximum percentage decrease in FEV_1 , time to recovery, and $AUC_{0-60\text{ min}}$ used an analysis of variance model with terms for patient, treatment, and period effect. The proportion of patients who required β -agonist rescue was compared between treatments using the McNemar test. In patients who required β -agonist rescue, the FEV_1 measurements obtained after β -agonist administration were excluded from the analyses. A step-down testing procedure was applied to account for the multiplicity of the 3 time points and of the secondary end points. Patients were also categorized by maximum percentage decrease in FEV_1 after exercise challenge (ie, patients whose FEV_1 decreased either $\leq 20\%$ or $>20\%$ of preexercise baseline, with similar categorical analyses defined by cutoffs

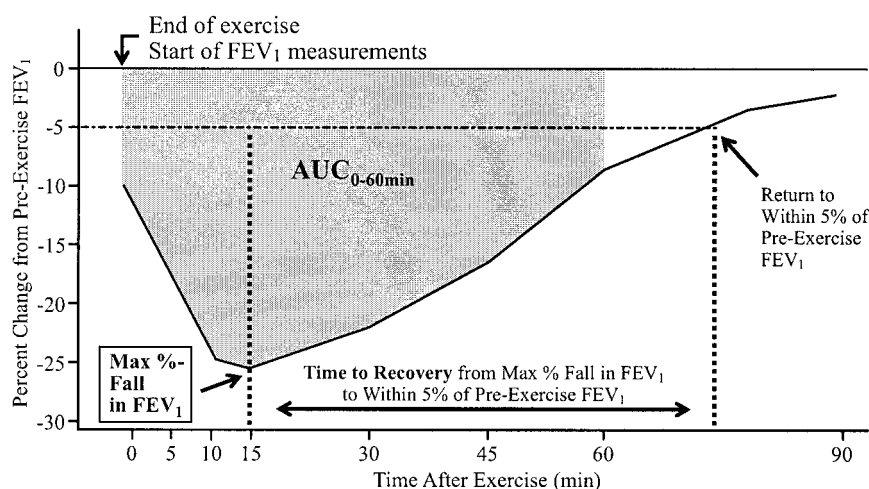


Figure 1. Schematic of major end points measured, showing hypothetical data for a single patient. Note that the larger the area under the curve for percentage decrease in forced expiratory volume in 1 second (FEV_1) during 60 minutes after exercise ($AUC_{0-60\text{ min}}$) (shaded area), the greater the intensity of exercise-induced bronchoconstriction.

of 15% and 10%) and compared by the McNemar test. All randomized patients were included in the safety analysis of clinical adverse experiences. The study had 95% power to detect an 8–percentage point difference between montelukast and placebo at the 2-hour challenge (with $\alpha = .05$, 2-sided test, and assumed within-patient SD of 9%) if 36 patients completed both treatment periods.

RESULTS

Patients and Baseline Characteristics

Of 169 patients screened for inclusion in the study, 118 patients were excluded and not randomized; 51 were randomized and 49 completed the study (Fig 2). Eighty-one patients did not qualify for randomization because their postexercise decrease in FEV₁ was less than 20% from their baseline. Two patients discontinued the study after randomization because of adverse experiences (asthma and influenza) while taking montelukast. Twenty-five patients were randomized to the montelukast followed by placebo sequence and 26 to the placebo followed by montelukast sequence. The number of patients who performed exercise challenges after both montelukast and placebo treatment was 49 at 2 hours, 48 at 12 hours, and 46 at 24 hours after dosing.

Baseline data for all randomized patients are given in Table 1, and prerandomization end point data are presented in Table 2. The mean preexercise FEV₁ was 86% of predicted at each visit. During the 2 prestudy visits, the mean maximum percentage decrease in FEV₁ from prechallenge baseline was 28% and 29%. Twelve percent of patients were taking in-

Table 1. Baseline Characteristics of Patients Before Randomization (N = 51)

Characteristics	No. (%) of patients*
Age, mean $\pm$ SD (range), y	24.5 $\pm$ 5.9 (16–39)
Female	27 (53)
Race	
White	41 (80)
Other	10 (20)
Duration of asthma, mean $\pm$ SD, y	13.8 $\pm$ 7.4
Patients taking inhaled corticosteroids	6 (12)

* Data are presented as number (percentage) of patients unless otherwise indicated.

haled corticosteroids at a stable and low dose for at least 5 weeks before randomization.

Efficacy

The primary end point of maximum percentage decrease in FEV₁ after exercise challenge at 2 hours was 10.8% $\pm$ 7.9% (mean $\pm$ SD) after montelukast and 22.3% $\pm$ 13.1% after placebo, significantly in favor of montelukast ($P \leq .001$). In addition, montelukast significantly reduced ($P \leq .001$) the maximum percentage decrease in FEV₁ after exercise challenge at 12 and 24 hours: 8.4% $\pm$ 7.5% and 8.3% $\pm$ 7.3% for montelukast vs 16.1% $\pm$ 10.2% and 16.9% $\pm$ 11.7% for placebo, respectively (Fig 3). The differences in least squares means (95% CIs) between the 2 treatments at 2, 12, and 24 hours were 11.5% (–14.7% to –0.3%), –7.7% (–10.5% to

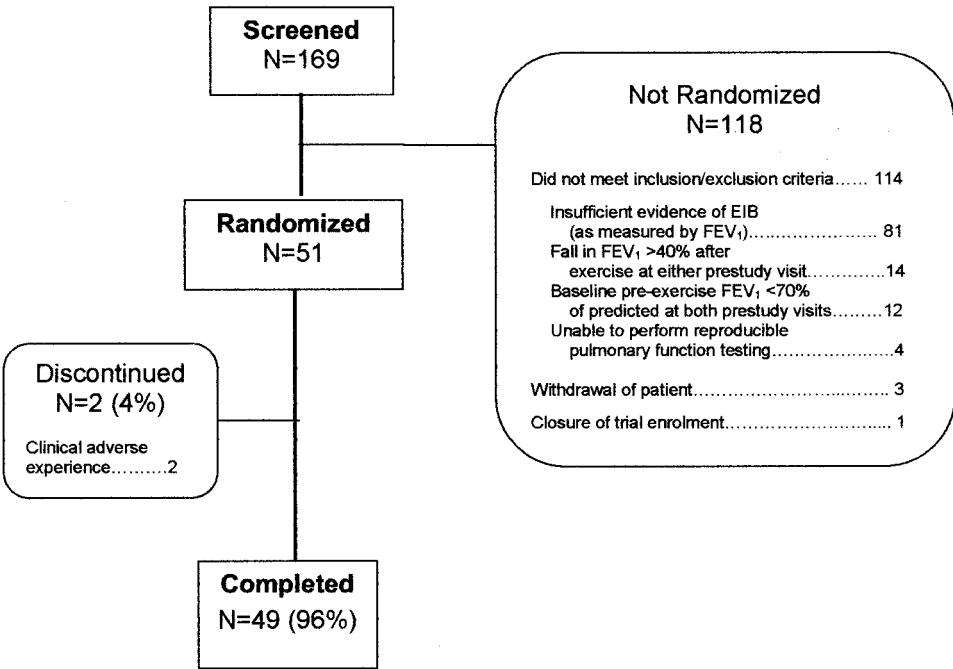


Figure 2. Patient disposition. EIB indicates exercise-induced bronchoconstriction; FEV₁, forced expiratory volume in 1 second.

Table 2. End Points Measured Before Randomization*

Factor	Prestudy visit 1 (n = 50†)	Prestudy visit 2 (n = 51)
Preexercise		
FEV ₁ , L	3.46 ± 0.7	3.46 ± 0.7
FEV ₁ , % predicted	85.97 ± 11.8	86.39 ± 11.9
Postexercise challenge		
Maximum decrease in FEV ₁ , %	28.96 ± 6.5	27.63 ± 5.6
AUC _{0-60min} , % × min	934.49 ± 515.3	762.59 ± 380.3
Time to recovery, min	50.19 ± 27.7	45.15 ± 29.7
Patients needing β-agonist rescue, No. (%)	7 (14)	4 (8)

Abbreviations: AUC_{0-60min}, area under the curve during the first 60 minutes after exercise challenge; FEV₁, forced expiratory volume in 1 second.

* Unless otherwise noted, all values are mean ± SD.

† Of 51 patients tested, measurements for 1 patient could not be obtained because of spirometry equipment failure; this patient was excluded from the analysis.

–4.9%), and –8.5% (–11.6% to –5.4%), respectively. Percentage of improvement in protection against EIB by montelukast, calculated relative to placebo as $100 \times ([\text{placebo} - \text{montelukast}]/\text{placebo})$, was 51.6%, 47.8%, and 50.6% at 2, 12, and 24 hours, respectively (Fig 3).

In prespecified subgroup analyses of the primary end point at 2 hours after dosing, the effect of montelukast was consistent between patients taking inhaled corticosteroid therapy and those who were not ($P = .55$). The mean ± SD maximum percentage decrease in FEV₁ for montelukast vs pla-

cebo in patients taking inhaled corticosteroids was 8.7 ± 4.1 vs 22.0 ± 12.3 for patients taking inhaled corticosteroids ($n = 6/49$) and 11.1 ± 8.3 vs 22.4 ± 13.3 for patients not taking inhaled corticosteroids ($n = 43/49$).

Patients taking montelukast showed a significantly quicker time to recovery after exercise challenges at 2, 12, and 24 hours than did patients taking placebo ($P \leq .001$ at all 3 time points) (Table 3). The least squares mean differences (95% CIs) between the 2 treatments were –26.8 minutes (–35.1 to –18.4 minutes), –16.0 minutes (–22.9 to –9.2 minutes), and –17.4 minutes (–24.9 to –9.9 minutes). The AUC_{0-60min} for percentage change in FEV₁ from preexercise baseline during the 60 minutes after exercise challenge at 2, 12, and 24 hours after dosing was significantly smaller (ie, less bronchoconstriction) in the montelukast group compared with the placebo group ($P \leq .001$) at all 3 time points (Table 3). Fewer patients taking montelukast than those taking placebo required rescue with a β-agonist within 90 minutes after exercise challenge at 2, 12, and 24 hours; at 2 hours, the difference between the 2 treatments was significant (Table 3).

In prespecified exploratory analyses, patients were categorized based on their maximum percentage decrease in FEV₁ as either 20% or less or greater than 20%. At exercise challenges 2 hours ($n = 49$), 12 hours ($n = 48$), and 24 hours after dosing ($n = 46$), statistically significantly ($P \leq .001$) more patients taking montelukast ($\geq 90\%$) than taking placebo ($\leq 60\%$) showed a maximum decrease in FEV₁ of 20% or less (Fig 4). Comparable results were seen in additional categorical analyses. At 2, 12, and 24 hours after dosing, the percentage of patients with a maximum decrease in FEV₁ of

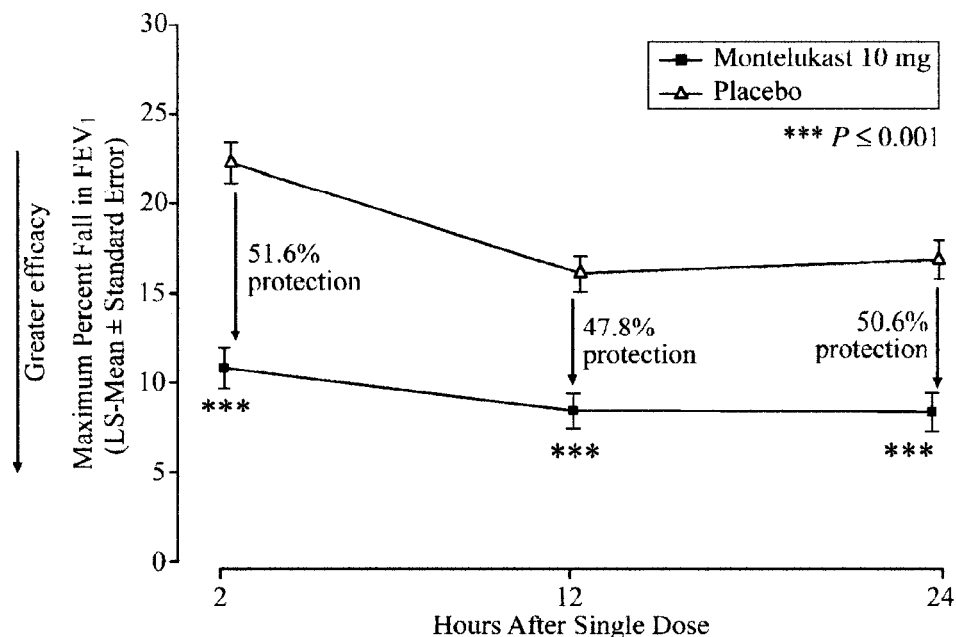


Figure 3. Maximum percentage decrease in forced expiratory volume 1 second (FEV₁) from preexercise baseline occurring within the first 60 minutes after exercise challenge at 2, 12, and 24 hours after dosing.

Table 3. Secondary End Points Measured After Exercise Challenges at 2, 12, and 24 Hours After Dosing*

Time of challenge after dosing	n	Montelukast	Placebo	Least squares mean difference (95% CI)
Time to Recovery From Maximum Percentage Decrease in FEV₁, min				
2 hours	49	10.82 ± 16.4	37.67 ± 32.4	-26.75 (-35.1 to -18.4)†
12 hours	48	7.97 ± 12.7	24.50 ± 25.7	-16.04 (-22.9 to -9.2)†
24 hours	46	5.74 ± 8.4	23.14 ± 26.1	-17.41 (-24.9 to -9.9)†
Area Under the Curve for FEV₁ Percentage Change From Preexercise Baseline, % × min				
2 hours	49	182.46 ± 235.9	702.13 ± 675.0	-517.1 (-678.5 to -355.6)†
12 hours	48	152.27 ± 179.5	389.55 ± 317.1	-232.2 (-317.7 to -146.8)†
24 hours	46	120.06 ± 119.8	409.50 ± 426.6	-289.4 (-408.3 to -170.6)†
No. (%) of Patients Requiring β-Agonist Rescue Medication After Exercise Challenge				
2 hours	49	1 (2)‡	7 (14)§	
12 hours	48	1 (2)‡	5 (10)	
24 hours	46	1 (2)‡	3 (7)	

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second.

* Data are presented as mean ± SD unless otherwise indicated.

† $\leq .001$.

‡ The single patient at each time point was not the same patient.

§ $P < .05$.

15% or less was 35%, 48%, and 43%, respectively, for patients taking placebo and 69%, 88%, and 85%, respectively, for patients taking montelukast ($P \leq .001$ at each time point). At 2, 12, and 24 hours, the percentage of patients with a maximum decrease in FEV₁ of 10% or less was 20%, 35%, and 33%, respectively, for patients taking placebo and 47%, 63%, and 67%, respectively, for patients taking montelukast ($P \leq .01$ at each time point).

Safety

The safety profile of montelukast in this single-dosing study was generally similar to that of placebo. No clinical adverse experiences were reported in 42 of the 51 randomized patients, and no serious clinical or laboratory adverse experiences were reported. Drug-related adverse experiences of nausea and nervousness were reported by 2 patients receiving montelukast; these were reported as moderate and mild, respectively, and both patients completed the study.

DISCUSSION

This study is the first, to our knowledge, to evaluate the effect of a single dose of an oral agent for acute prevention of EIB throughout 24 hours in adults with asthma. Our results show that montelukast was significantly effective in protecting against EIB after exercise challenge at 2, 12, and 24 hours after dosing, as measured by the end points of maximum percentage decrease in FEV₁, time to recovery, and the area under the curve for percentage change in FEV₁.

These results are consistent with and further expand on the results from other studies. In short-term (≤ 12 hours) studies in adult asthma, a single dose of montelukast demonstrated prompt and persistent protection against EIB induced by exercise challenge 1, 4, 8, and 12 hours after treatment in one study¹⁰ and 1 hour after treatment in another.²⁵ Several medium- and long-term, repeated-dosing studies have also demonstrated the consistent benefit of montelukast in signifi-

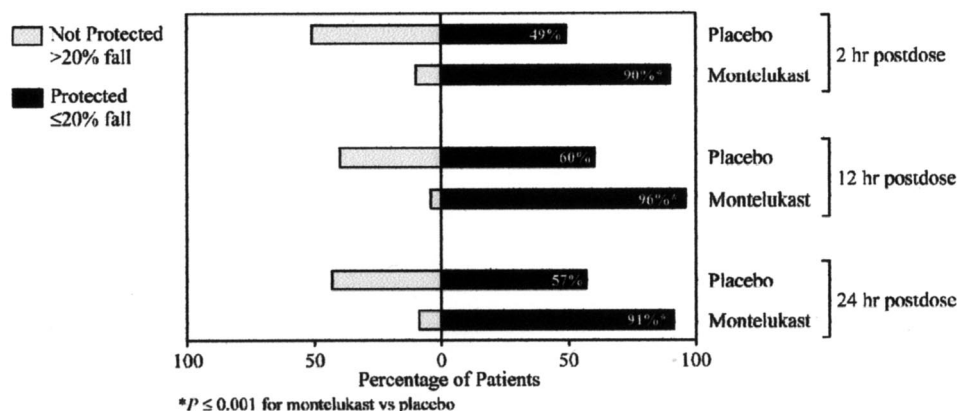


Figure 4. Percentage of patients protected from exercise-induced bronchoconstriction (maximum decrease in forced expiratory volume in 1 second of $\leq 20\%$) after exercise challenge at 2, 12, and 24 hours after dosing.

cantly attenuating EIB. Bronsky et al²⁶ demonstrated efficacy of montelukast in protecting against EIB at the end of the 24-hour dosing interval after 2 once-daily doses. Once-daily treatment with montelukast provided stable protection against EIB during a 12-week period in adult asthmatic patients.¹⁸

Our results indicate that protection against EIB by a single dose of montelukast is clinically meaningful during a 2- to 24-hour period. First, significantly fewer patients taking montelukast than those taking placebo required rescue with a β -agonist within the 90 minutes after exercise at 2 hours after receiving a single dose. Second, in an exploratory analysis, patients were categorized in each treatment into 2 groups: those whose response to exercise was reduced to a decrease in FEV₁ of 20% or less (ie, reduced from the level of EIB that was required for study entry) vs those whose response remained more than 20%. The results showed that significantly more patients taking montelukast than those taking placebo were protected (FEV₁ decrease of $\leq 20\%$) at all 3 time points after dosing. Some investigators have defined EIB as a post-exercise decrease in FEV₁ of 15% or 10%.^{1,27,28} Our additional categorical analyses used both of these cutoffs and showed that, no matter which cutoffs were used, significantly more patients taking montelukast than those taking placebo were protected from EIB at all 3 time points. Finally, it has been proposed that an improvement in percentage decrease in FEV₁ of 50% or greater relative to the placebo decrease may be defined as clinically important.^{29,30} In patients with a prebronchodilator decrease in FEV₁ of less than 40% from preexercise baseline, montelukast provided protection of 48% to 52% relative to the placebo decrease across the 3 time points; consistent with this definition, the results of this study demonstrate a clinically important level of protection against EIB.

The levels of EIB that were elicited after randomization were relatively mild, especially at 12 and 24 hours after a single dose. Reduced levels of EIB at the later time points are not likely due to a refractory period, because the span between challenges was sufficient.^{31–33} Thus, although a maximal decrease in FEV₁ of 20% or greater on 2 occasions was required for study entry, many patients did not demonstrate this level of decrease after randomization, including those receiving placebo treatment. In a post hoc analysis, the maximum percentage decrease at 12 or 24 hours after placebo was significantly less than at 2 hours after placebo. This reduced response to exercise (ie, mean maximal decrease was $<20\%$ at both 12 and 24 hours after placebo) shows that important variation in exercise response can occur even in patients with documented reproducible EIB. This finding is consistent with previous reports of reduced levels of EIB with placebo treatment.^{11,23,34} Nevertheless, the treatment effect of montelukast was readily demonstrated despite the overall reduced exercise responses seen after randomization (including at 12 and 24 hours after placebo).

Although this study shows significant protection by montelukast compared with placebo, a limitation of this study is the absence of an active comparator. Of note, a previous report¹⁰ showed that montelukast and salmeterol provided

similar levels of protection against EIB up to 12 hours after a single dose. An avenue for future research is to compare the efficacy of these treatments throughout the 24 hours after a single dose. Importantly, although salmeterol and formoterol provide protection against EIB for up to 12 hours after a single dose, the duration of their protective effect declines when given regularly.^{20,35,36} In 2 separate studies comparing chronic dosing of montelukast and salmeterol, the broncho-protective effect of montelukast was maintained throughout the 8 weeks of study, whereas a significant loss of protection (tachyphylaxis) occurred with salmeterol at weeks 4 and 8.^{19,37} Thus, 24-hour protection against EIB by oral montelukast, as demonstrated in this single-dose study and as maintained with chronic dosing (as long as 12 weeks in a previous study),¹⁸ provides meaningful clinical benefit, particularly for patients who exercise regularly and/or at different times of the day and therefore need frequent (perhaps daily) use of EIB prevention therapy, as well as for those with irregularly anticipated opportunities for exercise.

In summary, we have shown that a single oral dose of montelukast demonstrated significant protection against EIB, as reflected by several measures, including the level of improvement in response and the proportion of patients protected against EIB. The protective benefit of montelukast was evident by 2 hours and persisted throughout 24 hours, suggesting a potentially clinically important benefit of montelukast when used for acute prevention of exercise-induced bronchoconstriction.

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