

## MONTELUKAST, A LEUKOTRIENE-RECEPTOR ANTAGONIST, FOR THE TREATMENT OF MILD ASTHMA AND EXERCISE-INDUCED BRONCHOCONSTRICTION

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### ABSTRACT

**Background** Patients with mild asthma frequently have only exercise-induced bronchoconstriction, a symptom of inadequate control of asthma. We evaluated the ability of montelukast, a leukotriene-receptor antagonist, to protect such patients against exercise-induced bronchoconstriction.

**Methods** We randomly assigned 110 patients (age, 15 to 45 years) with mild asthma and a decrease in the forced expiratory volume in one second (FEV<sub>1</sub>) of at least 20 percent after exercise on two occasions during a placebo run-in period to receive 10 mg of montelukast (54 patients) or placebo (56 patients) once daily at bedtime for 12 weeks in a double-blind study. Treatment was followed by a two-week, single-blind washout period during which all patients received placebo. Exercise challenges were performed at base line; 20 to 24 hours after dosing at weeks 4, 8, and 12; and at the end of the washout period. The primary end point was the area under the curve for FEV<sub>1</sub> (expressed as the percent change from base-line values) in the first 60 minutes after exercise. This measure summarized the extent and duration of bronchoconstriction after exercise.

**Results** At 12 weeks, montelukast therapy offered significantly greater protection against exercise-induced bronchoconstriction than placebo therapy (expressed as the percentage of inhibition of the end points), as evidenced by the improvement in the area under the FEV<sub>1</sub> curve (degree of inhibition, 47.4 percent; P=0.002). Montelukast therapy was also associated with a significant improvement in the maximal decrease in FEV<sub>1</sub> after exercise (P=0.003) and the time from the maximal decrease in FEV<sub>1</sub> to the return of lung function to within 5 percent of pre-exercise values (P=0.04). The differences between groups in the various measures of lung function were similar at 4, 8, and 12 weeks; there was no evidence of rebound worsening of lung function in the montelukast group after the washout period. After 12 weeks of treatment, patients in the montelukast group were more likely to rate their asthma control as better and less likely to require rescue therapy with a  $\beta$ -agonist during or after exercise challenge. The rates of adverse events were similar in the two groups.

**Conclusions** As compared with placebo, once-daily treatment with montelukast provided significant protection against exercise-induced asthma over a 12-week period. Tolerance to the medication and rebound worsening of lung function after discontinuation of treatment were not seen. (N Engl J Med 1998;339:147-52.)

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**E**XERCISE-INDUCED bronchoconstriction is common among adults with mild-to-severe asthma, limiting activity and worsening the quality of life.<sup>1</sup> The presence of airway hyperresponsiveness to exercise suggests a lack of control of asthma. Accordingly, the degree of protection afforded by a drug against exercise-induced bronchoconstriction may be used to assess therapeutic benefit in patients with mild asthma who have near-normal airway function and minimal symptoms.

The cause of exercise-induced bronchoconstriction is incompletely understood, although airway cooling and drying are hypothesized to stimulate the release of inflammatory mediators such as the cysteinyl leukotrienes (leukotriene C<sub>4</sub>, D<sub>4</sub>, and E<sub>4</sub>),<sup>1</sup> which are excreted in urine as leukotriene E<sub>4</sub> (a stable metabolite of leukotriene C<sub>4</sub> and D<sub>4</sub>) after exercise challenge.<sup>2,3</sup> Inhibitors of the synthesis of leukotriene<sup>4,5</sup> and leukotriene-receptor antagonists<sup>3,6-9</sup> have been shown to protect against exercise-induced bronchoconstriction.

Montelukast is a potent, specific antagonist of leukotriene receptors<sup>10,11</sup> that was recently approved in the United States and other countries for the treatment of chronic asthma. The protective effects of two doses of montelukast on exercise-induced bronchoconstriction have been shown at 20 to 24 hours after dosing.<sup>3,7</sup> In a 12-week, placebo-controlled study, we evaluated the effect of once-daily montelukast on airway hyperresponsiveness to exercise and methacholine challenges and on the overall clinical condition of patients with mild asthma.

### METHODS

#### Patients

After screening about 250 patients, we recruited 110 nonsmoking patients (age, 15 to 45 years) who had had asthma for more than one year, were using only inhaled  $\beta$ -agonists, had a decrease

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in the forced expiratory volume in one second (FEV<sub>1</sub>) of 20 percent or more in response to a challenge with methacholine ( $\leq 4$  mg per milliliter), and had a decrease in FEV<sub>1</sub> of 20 percent or more after a standardized exercise challenge on two occasions. All patients were in good health on the basis of medical history, physical examination, and routine laboratory tests. All patients had quit smoking at least one year before the study and had a history of no more than 7 pack-years of smoking.

Patients were not eligible for the study if they had been treated for asthma in an emergency room within one month before the study, had been hospitalized for asthma within three months before the study, had had an unresolved upper respiratory tract infection within six weeks before the study, or had had an unresolved sinus infection within one week before the study. The use of corticosteroids, long-acting antihistamines, theophylline, oral or long-acting  $\beta$ -adrenergic agonists, inhaled anticholinergic agents within one month before the study, and the use of cromolyn or nedocromil within two weeks before the study were also reasons for exclusion. Immunotherapy at a constant dose was allowed. Treatment with short-acting antihistamines and inhaled  $\beta$ -agonists was permitted as needed, except in the 48 hours and 6 hours, respectively, before scheduled clinic visits. Caffeinated beverages were not permitted in the eight hours before visits.

Patients were withdrawn from the study if treatment was interrupted for more than six consecutive days, if treatment with an excluded medication was initiated, in the event of pregnancy, or in the event of worsening asthma that required treatment with corticosteroids.

The protocol was approved by the institutional review boards of all participating centers, and written informed consent was obtained from all participants. The study was conducted between May 11 and December 6, 1995.

### Study Design

This randomized, double-blind, placebo-controlled, parallel-group trial was conducted at six centers. After a 1-week, single-blind, base-line period during which patients received placebo once daily, patients were randomly assigned to receive 10 mg of montelukast (Singulair, Merck, West Point, Pa.) or matching placebo, with or without food, once daily at bedtime for 12 weeks. All exercise challenges were performed 20 to 24 hours after the bedtime dose (the trough of the dosing interval) during the base-line period and 4, 8, and 12 weeks after treatment began. Methacholine challenge was performed during the base-line period and at 4 and 12 weeks on days on which exercise challenge was not performed. After a two-week washout period during which time all patients received placebo in a single-blind fashion, exercise and methacholine challenges were again performed.

### Exercise Challenge

After a two-minute warmup, patients exercised for six minutes on a treadmill while inhaling compressed dry air at room temperature through a face mask, at a workload that increased the heart rate to 80 to 90 percent of the age-predicted maximum (calculated as  $220 - \text{age}$ ). Every effort was taken to perform exercise challenges at the same time of day. Small adjustments in workload (treadmill speed or grade) were made, if necessary, to achieve targeted heart rates. The FEV<sub>1</sub> before exercise was calculated as the mean of measurements performed 20 and 5 minutes before exercise and was required to be at least 65 percent of the predicted value for the exercise challenge to proceed. Spirometry was performed 0, 5, 10, 15, 30, 45, and 60 minutes after exercise. If by 60 minutes the FEV<sub>1</sub> had not returned to within 5 percent of the pre-exercise value, additional measurements were obtained 75 minutes and, if necessary, 90 minutes after exercise. At the discretion of the investigator, patients could receive an inhaled  $\beta$ -agonist for distressing symptoms at any time during or after exercise challenge. Patients maintained their usual pattern of activities, except they refrained from strenuous exercise for at least 18 hours before exercise challenge.

### Methacholine Challenge

To assess nonspecific bronchial hyperresponsiveness, methacholine challenge was performed between 6 and 10 a.m. with a nebulizer (model 646, DeVilbiss, Somerset, Pa.) and a dosimeter (Scientific and Medical Instrument Co., Doylestown, Pa.)<sup>12</sup> whose standard output was within 15 percent of the median output. Patients used the same nebulizer throughout the study. The concentration of methacholine required to decrease the FEV<sub>1</sub> by 20 percent (PC<sub>20</sub>) was measured. Patients received 0.156 mg of methacholine per milliliter initially, and concentrations were then doubled (up to a maximum of 25 mg per milliliter) at intervals of five minutes until a decrease in FEV<sub>1</sub> of 20 percent or more occurred. The PC<sub>20</sub> was computed from the methacholine dose-response curve (the change in FEV<sub>1</sub> in relation to the methacholine concentration) by linear interpolation on a log scale. Methacholine solutions were prepared by one central pharmacy.

### Spirometry

A standard spirometer (model PB-100/110, Puritan Bennett, Lenexa, Kans.) was used at each study site. Patients were encouraged to perform at least three maneuvers during each measurement to meet American Thoracic Society criteria for acceptability and reproducibility.<sup>13</sup> The largest FEV<sub>1</sub> value from each set of measurements was used for analysis. Spirometry training and quality control were centralized.

### Global Assessment of Asthma Control

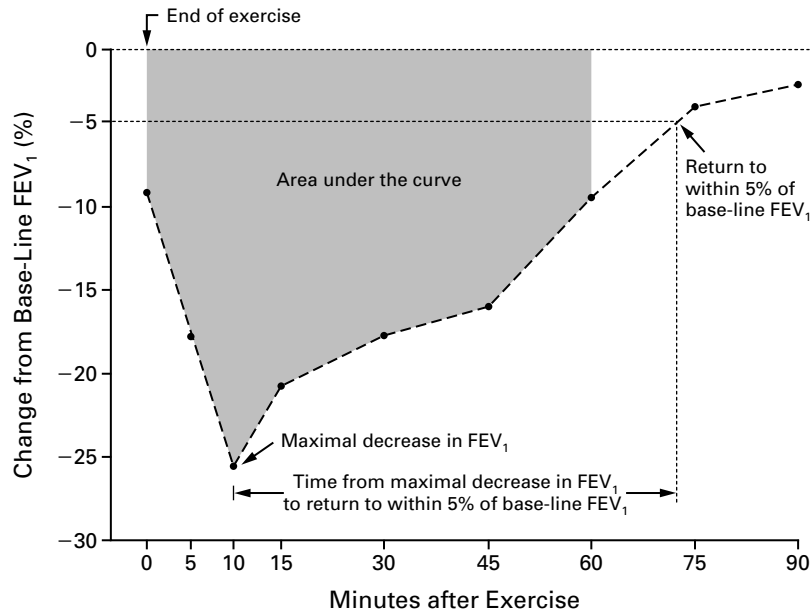
Patients evaluated the overall control of asthma after the 12-week treatment period by using a seven-point scale to answer the following question: "Since the beginning of the study, my asthma is now very much better (score, 0), much better (1), better (2), the same (3), worse (4), much worse (5), or very much worse (6)."

### Statistical Analysis

The primary end point was the area under the curve (AUC) for FEV<sub>1</sub> (expressed as the percent change from base-line values) in the first 60 minutes after exercise challenge, summarizing the extent and duration of bronchoconstriction after exercise (Fig. 1). The maximal decrease in FEV<sub>1</sub> after exercise and the length of time from the maximal decrease in FEV<sub>1</sub> to the return to within 5 percent of the FEV<sub>1</sub> value measured before exercise were secondary end points.

If a  $\beta$ -agonist was administered as rescue therapy after an exercise challenge, subsequent FEV<sub>1</sub> values were excluded; the last FEV<sub>1</sub> measurement before rescue therapy was carried forward. In such a case, the maximal decrease in FEV<sub>1</sub> was calculated from the lowest value recorded before  $\beta$ -agonist rescue. If rescue therapy was administered after exercise or if the FEV<sub>1</sub> did not recover to within 5 percent of base line within 90 minutes after exercise, the time to recovery was defined as 100 minutes. If the FEV<sub>1</sub> did not drop below 95 percent of the base-line value, the time to recovery was defined as zero.

The change in values from the second of the two exercise challenges conducted before treatment to week 12 of treatment was analyzed for all end points. When a measurement at week 12 was not recorded, the measurement from week 8 or week 4 (if the value for week 8 was also missing) was used in an analysis-of-variance model,<sup>14</sup> with factors for center and treatment. We assessed the consistency of the protective effects by including pre-exercise FEV<sub>1</sub> values and the interaction between treatment and pre-exercise FEV<sub>1</sub> values in the analysis-of-variance model. Significance testing was also performed at weeks 4 and 8. The degree of protection against bronchoconstriction afforded by montelukast therapy, as compared with placebo treatment, was expressed, for each end point, as the percentage of inhibition induced by montelukast therapy, and was calculated with the following equation:  $100 \times (1 - \text{mean response to montelukast therapy} \div \text{mean response to placebo treatment})$ . We assessed tolerance by comparing the slopes of the changes in values between treatment groups



**Figure 1.** End Points Used to Assess the Degree of Exercise-Induced Bronchoconstriction. The following end points were assessed: the area under the curve for the percent decrease in FEV<sub>1</sub> in the first 60 minutes after exercise, the maximal decrease in FEV<sub>1</sub> after exercise, and the time from the maximal decrease in FEV<sub>1</sub> to the return to within 5 percent of the FEV<sub>1</sub> value before exercise.

for the three end points over the 12-week treatment period using a mixed-effects model,<sup>15</sup> which takes into account variability within and between patients.

For the methacholine challenge, we used the same analysis-of-variance model to analyze the change in PC<sub>20</sub> values over time. The patients' global assessment of asthma control was analyzed with a Cochran–Mantel–Haenszel test for ordered categorical data. The seven-point scale was reduced to three categories for the purposes of analysis: “better” (a score of 0, 1, or 2), “no change” (a score of 3), or “worse” (a score of 4, 5, or 6). Fisher’s exact test was used to compare differences between groups in the proportion of patients requiring β-agonist rescue therapy at each visit.

We used an intention-to-treat approach, including all patients with a base-line measurement and at least one subsequent measurement, for all exercise and PC<sub>20</sub> end points. All significance testing was two-tailed; a P value of 0.05 or less was considered to indicate statistical significance.

A total of 80 patients (40 patients in each group) was required in order to detect at a power of 90 percent a difference of 50 percent in the AUC between the two treatment groups. The power calculation was based on the variability observed in previous montelukast exercise-challenge studies.<sup>3,7</sup>

**RESULTS**

**Randomization and Withdrawal**

Of the 110 patients enrolled in the study, 56 were randomly assigned to the placebo group and 54 to the montelukast group. There were no clinically important demographic differences between the two groups (Table 1). Thirteen patients did not complete the study: seven in the placebo group and six in the montelukast group. In the placebo group, four pa-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS.\***

CHARACTERISTIC	PLACEBO GROUP (N=56)	MONTELUKAST GROUP (N=54)
Age (yr)		
Mean	25	25
Range	15–45	15–39
Male sex (%)	51.8	51.9
Duration of asthma (yr)	14±7.5	16±9.0
Pre-exercise FEV <sub>1</sub> (% of predicted)	83.5±11.0	83.2±10.9
Exercise challenge		
Area under FEV <sub>1</sub> curve (% change · min)	1577±930	1396±822
Maximal decrease in FEV <sub>1</sub> after exercise (%)	38.5±11.8	36.7±11.2
Time from maximal decrease in FEV <sub>1</sub> to return to within 5% of base-line FEV <sub>1</sub> (min)	65.8±32.7	64.1±31.7
PC <sub>20</sub> (mg/ml)	0.45±0.35	0.46±0.41
History of allergic rhinitis (%)	89.3	92.6

\*Plus–minus values are means ±SD. FEV<sub>1</sub> denotes forced expiratory volume in one second, and PC<sub>20</sub> the concentration of methacholine required to decrease the FEV<sub>1</sub> by 20 percent.

tients stopped treatment because of worsening asthma, two were withdrawn because of protocol deviations, and one withdrew consent. In the montelukast group, one patient stopped treatment because of sinusitis, one patient stopped treatment because of respiratory distress, one stopped treatment because

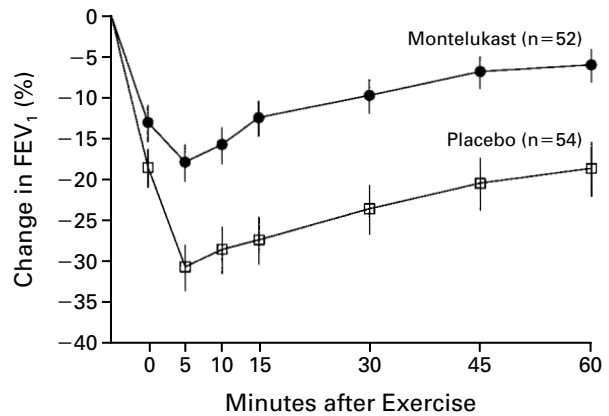
of pregnancy, one was withdrawn because of a protocol deviation, one was lost to follow-up, and one withdrew consent.

Two patients in each group had only base-line exercise data and were excluded from the exercise analysis. Two patients in the placebo group and one patient in the montelukast group had only base-line data on methacholine challenge and were excluded from methacholine analysis.

**Effect of Montelukast on Exercise-Induced Bronchoconstriction**

The mean ( $\pm$ SD) FEV<sub>1</sub> before exercise was similar in the placebo and montelukast groups at the second base-line measurement ( $3.33 \pm 0.69$  and  $3.35 \pm 0.66$  liters, respectively) and at week 12 ( $3.33 \pm 0.71$  and  $3.45 \pm 0.65$  liters, respectively).

The degree of protection against bronchoconstriction afforded by montelukast therapy at week 12 was significantly greater than that offered by placebo treatment (Fig. 2 and Table 2). Montelukast therapy was associated with a significant improvement in the AUC (degree of inhibition as compared with placebo, 47.4 percent;  $P=0.002$ ). There was no significant interaction between treatment and pre-exercise FEV<sub>1</sub> values, indicating that the protective effect of montelukast was consistent among the patients. Twelve weeks of therapy with montelukast was also associated with significant improvements in the maximal decrease in FEV<sub>1</sub> after exercise ( $P=0.003$ ) and the time from the maximal decrease in FEV<sub>1</sub> to



**Figure 2.** Mean ( $\pm$ SE) Changes in FEV<sub>1</sub> after Exercise Challenge after 12 Weeks of Treatment with Montelukast or Placebo. Treatment with montelukast was associated with a significant ( $P=0.002$ ) reduction in exercise-induced bronchoconstriction.

the return to within 5 percent of pre-exercise FEV<sub>1</sub> ( $P=0.04$ ) (Table 2). Three patients in the placebo group (6 percent) and 12 patients in the montelukast group (23 percent) had a maximal decrease in FEV<sub>1</sub> of less than 10 percent at 12 weeks, and 31 patients (57 percent) and 13 patients (25 percent), respectively, had a maximal decrease in FEV<sub>1</sub> of more than 30 percent.

During the 12-week treatment period, the differences between groups in the various measures re-

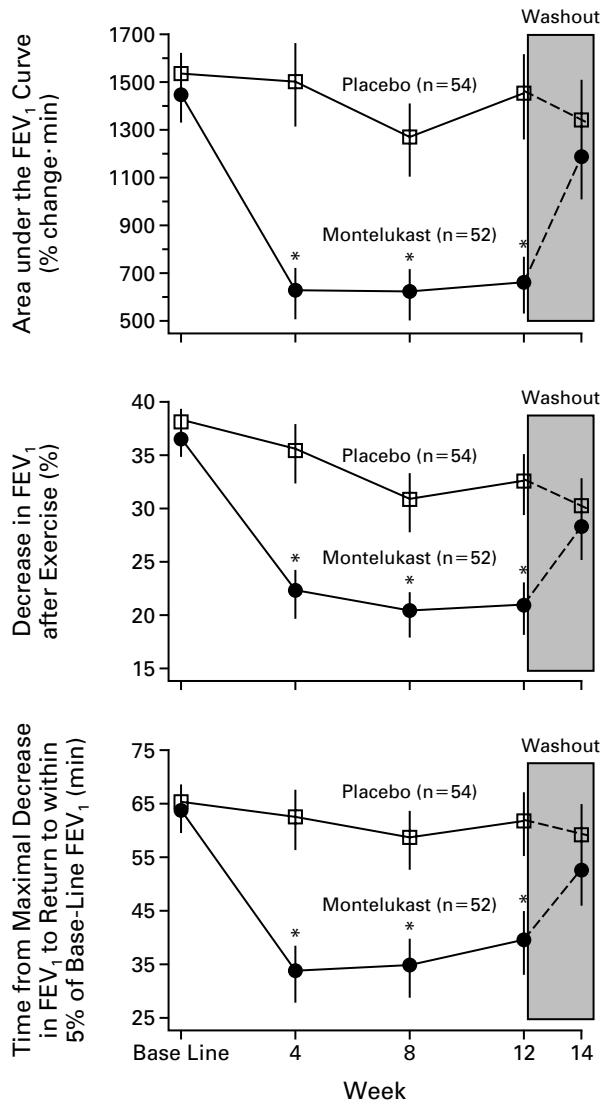
**TABLE 2.** ANALYSIS OF END POINTS AT THE END OF 12 WEEKS OF TREATMENT.\*

END POINT	MEAN BASE-LINE VALUE	MEAN VALUE DURING TREATMENT	95% CI FOR CHANGE FROM BASE LINE	PERCENT INHIBITION†	P VALUE‡	95% CI FOR THE DIFFERENCE BETWEEN TREATMENT GROUPS
Area under FEV <sub>1</sub> curve (% change · min)						
Placebo	1593	1441	-376 to 66			
Montelukast	1407	758	-888 to -436	47.4	0.002	-818 to -196
Maximal decrease in FEV <sub>1</sub> (%)						
Placebo	38.9	32.4	-9.7 to -2.8			
Montelukast	36.5	22.2	-17.3 to -10.2	31.6	0.003	-12.4 to -2.6
Time from maximal decrease in FEV <sub>1</sub> to return to within 5% of base-line FEV <sub>1</sub> (min)						
Placebo	66.5	60.6	-14.4 to 5.1			
Montelukast	64.6	44.3	-29.3 to -9.4	26.9	0.04	-28.4 to -1.0

\*Data on 54 patients in the placebo group and 52 patients in the montelukast group were analyzed. CI denotes confidence interval.

†The degree of protection against bronchoconstriction was expressed as the percentage of inhibition of the end points induced by montelukast therapy, as compared with placebo, and was calculated with the following equation:  $100 \times (1 - \text{mean response to montelukast therapy} \div \text{mean response to placebo})$ .

‡The P value is for the comparison with placebo.



**Figure 3.** Effects of Treatment with Montelukast and Placebo on the Three End Points over Time.

During the two-week washout period, all patients received placebo in a single-blind fashion. Values are means  $\pm$  SE. Asterisks indicate significant differences ( $P < 0.05$ ) between groups.

mained stable (Fig. 3). Two weeks after the cessation of therapy, the mean values in the montelukast group approached those in the placebo group (Fig. 3).

**Global Assessment of Asthma Control and Use of  $\beta$ -Agonist Rescue Therapy after Exercise Challenge**

Twelve weeks of montelukast therapy significantly improved the control of asthma, as determined by the patients' global assessment scores ( $P = 0.009$ ). In the montelukast group, 73.1 percent of patients characterized the control of asthma as better, 21.2 percent as unchanged, and 5.8 percent as worse, as

compared with respective values of 44.4 percent, 46.3 percent, and 9.3 percent in the placebo group. Significantly fewer patients in the montelukast group than in the placebo group required rescue therapy with a  $\beta$ -agonist after exercise challenge at each visit during the treatment period. The respective values for the montelukast and placebo groups were 7.8 percent and 27.8 percent at week 4, 8.0 percent and 24.5 percent at week 8, and 14.3 percent and 36.0 percent at week 12 ( $P < 0.05$  for all comparisons).

**Methacholine Challenge**

The mean PC<sub>20</sub> values in the montelukast group and the placebo group were similar at base line ( $0.46 \pm 0.41$  vs.  $0.45 \pm 0.35$  mg per milliliter). During the methacholine challenge, patients in the montelukast group required proportionately more doubling doses than patients in the placebo group (0.45 vs. 0.14), but the difference between the two groups was not significant ( $P = 0.16$ ).

**Adverse Effects**

There were no significant differences between groups in the frequency of clinical or laboratory adverse effects. The three most commonly reported adverse effects were headache (32 percent of patients in the placebo group, as compared with 20 percent of patients in the montelukast group), upper respiratory tract infections (23 percent vs. 28 percent), and worsening asthma (10 percent vs. 4 percent). One patient in each group had elevations in serum aminotransferase levels to more than three times the upper limit of normal. In each case, the elevations were transient and self-limiting. Withdrawal of montelukast during the washout period did not cause an increased incidence of worsening asthma as compared with placebo.

**DISCUSSION**

We found that once-daily treatment with 10 mg of montelukast, as compared with placebo, provided significant protection against exercise-induced bronchoconstriction over a 12-week period. Although previous studies involving exercise challenge showed that once-daily treatment with montelukast exerted a dose-related protective effect at the end of the dosing interval after the second dose,<sup>3,7</sup> we found that long-term therapy at the 10-mg dose provided consistent protection. The absence of a diminution in the degree of protection against exercise-induced bronchoconstriction after long-term therapy due to the development of tolerance differentiates montelukast therapy from other therapies. For example, tolerance develops after one week of treatment with a short-acting inhaled  $\beta$ -agonist, albuterol,<sup>16</sup> and the degree of tolerance that develops is similar to that occurring after four weeks of treatment with the

long-acting  $\beta$ -agonist salmeterol.<sup>17,18</sup> In a placebo-controlled study of exercise-induced bronchoconstriction in children who were seven to nine years of age, 12 weeks of inhaled beclomethasone (400  $\mu$ g daily) resulted in significant improvement of asthma control at 1 and 2 months; however, tolerance to the drug had developed by 3 months.<sup>19</sup> In addition, in a crossover study of a different leukotriene-receptor antagonist (cinalukast), tolerance to the lowest dose, but not higher doses, developed after one week of therapy.<sup>20</sup> The leukotriene antagonism induced by this compound may have caused up-regulation of leukotriene receptors, an effect overcome by higher doses.<sup>20</sup>

The magnitude of protection against exercise-induced bronchoconstriction afforded by montelukast in our study is consistent with that reported in other studies.<sup>3,7</sup> A previous experimental leukotriene-receptor antagonist demonstrated more complete protection,<sup>6</sup> but exercise-induced bronchoconstriction at base line was less severe in that trial than in ours (mean decrease in FEV<sub>1</sub>, 25 percent vs. 37 percent), which may account for the differences in results.

Although there was no residual protective effect of montelukast two weeks after treatment was stopped, neither was there rebound worsening of exercise-induced bronchoconstriction. This absence of rebound worsening is consistent with the effect of the drug on other clinical measures of asthma control reported in previous trials after the cessation of treatment.<sup>21-23</sup>

In addition, montelukast therapy had very few adverse effects, as has been found in clinical trials after up to three months of treatment<sup>21-23</sup> and in limited numbers of patients after up to one year of therapy.<sup>24</sup>

Although patients in the montelukast group had a significant improvement in PC<sub>20</sub> as compared with base-line values, the difference between groups was not significant. The 12-week treatment period may have been too short to induce a change in nonspecific hyperresponsiveness; in studies of inhaled glucocorticoids a treatment period of 6 months is frequently required for such changes to become apparent.<sup>25</sup> It is also possible that a small but undetectable effect occurred or that because the patients had relatively mild asthma, the initial hyperresponsiveness may not have been severe enough to show significant improvement with montelukast therapy.

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## REFERENCES

- McFadden ER Jr, Gilbert IA. Exercise-induced asthma. *N Engl J Med* 1994;330:1362-7.
- Kikawa Y, Miyanomae T, Inoue Y, et al. Urinary leukotriene E<sub>4</sub> after exercise challenge in children with asthma. *J Allergy Clin Immunol* 1992; 89:1111-9.
- Reiss TF, Hill JB, Harman E, et al. Increased urinary excretion of LTE<sub>4</sub> after exercise and attenuation of exercise-induced bronchospasm by montelukast, a cysteinyl leukotriene receptor antagonist. *Thorax* 1997;52:1030-5.
- Williams J, Gierczak S, Meltzer S, Nadel A, Jungerwirth S, Bleeker E. Effect of the leukotriene synthesis inhibitor BAY y 1015 on exercise-induced bronchospasm in patients with asthma. *Am J Respir Crit Care Med* 1996;153:Suppl:A803. abstract.
- Meltzer SS, Hasday JD, Cohn J, Bleeker ER. Inhibition of exercise-induced bronchospasm by zileuton: a 5-lipoxygenase inhibitor. *Am J Respir Crit Care Med* 1996;153:931-5.
- Manning PJ, Watson RM, Margolske DJ, Williams VC, Schwartz JJ, O'Byrne PM. Inhibition of exercise-induced bronchoconstriction by MK-571, a potent leukotriene D<sub>4</sub>-receptor antagonist. *N Engl J Med* 1990;323:1736-9.
- Bronsky EA, Kemp JP, Zhang J, Guerreiro D, Reiss TF. Dose-related protection of exercise bronchoconstriction by montelukast, a cysteinyl leukotriene-receptor antagonist, at the end of a once-daily dosing interval. *Clin Pharmacol Ther* 1997;62:556-61.
- Makker HK, Lau LC, Thomson HW, Binks SM, Holgate ST. The protective effect of inhaled leukotriene D<sub>4</sub> receptor antagonist ICI 204,219 against exercise-induced asthma. *Am Rev Respir Dis* 1993;147:1413-8.
- Kemp JP, Dockhorn RJ, Shapiro GG, et al. Montelukast, a leukotriene receptor antagonist, inhibits exercise-induced bronchoconstriction in 6- to 14-year old children. *J Allergy Clin Immunol* 1997;99:S321. abstract.
- Jones TR, Labelle M, Belley M, et al. Pharmacology of montelukast sodium (Singulair), a potent and selective leukotriene D<sub>4</sub> receptor antagonist. *Can J Physiol Pharmacol* 1995;73:191-201. [Erratum, *Can J Physiol Pharmacol* 1995;73:747.]
- De Leppeleire I, Reiss TF, Rochette F, et al. Montelukast causes prolonged, potent leukotriene D<sub>4</sub>-receptor antagonism in the airways of patients with asthma. *Clin Pharmacol Ther* 1997;61:83-92.
- Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness: standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J* 1993;16:53-83.
- Standardization of spirometry: 1994 update. *Am J Respir Crit Care Med* 1995;152:1107-36.
- Snedecor GW, Cochran WG. *Statistical methods*. 8th ed. Ames: Iowa State University Press, 1989:299-325.
- Laird NM, Ware JH. Random-effects model for longitudinal data. *Biometrics* 1982;38:963-74.
- Inman MD, O'Byrne PM. The effect of regular inhaled albuterol on exercise-induced bronchoconstriction. *Am J Respir Crit Care Med* 1996; 153:65-9.
- Ramage L, Lipworth BJ, Ingram CG, Cree IA, Dhillon DP. Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respir Med* 1994;88:363-8.
- Bhagat R, Kalra S, Swystun VA, Cockcroft DW. Rapid onset of tolerance to the bronchoprotective effect of salmeterol. *Chest* 1995;108:1235-9. [Erratum, *Chest* 1996;109:592.]
- Freezer NJ, Croasdell H, Doull IJM, Holgate ST. Effect of regular inhaled beclomethasone on exercise and methacholine airway responses in school children with recurrent wheeze. *Eur Respir J* 1995;8:1488-93.
- Adelroth E, Inman MD, Summers E, Pace D, Modi M, O'Byrne PM. Prolonged protection against exercise-induced bronchoconstriction by the leukotriene D<sub>4</sub>-receptor antagonist cinalukast. *J Allergy Clin Immunol* 1997;99:210-5.
- Altman LC, Munk Z, Seltzer J, et al. A placebo controlled, dose ranging study of montelukast, a cysteinyl leukotriene receptor antagonist. *J Allergy Clin Immunol* (in press).
- 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;158:1213-20.
- Noonan MJ, Chervinsky P, Brandon M, et al. Montelukast, a potent cysteinyl leukotriene antagonist, causes dose related improvements in chronic asthma. *Eur Respir J* (in press).
- Knorr B, Noonan G, McBurney J, et al. Evaluation of the safety profile of montelukast (MK-0476) in adult and pediatric patients (aged 6 to 14 years). *Eur Respir J* (in press). abstract.
- Simons FER, Canadian Beclomethasone Dipropionate-Salmeterol Xinafoate Study Group. A comparison of beclomethasone, salmeterol, and placebo in children with asthma. *N Engl J Med* 1997;337:1659-65.