A comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge

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Summary Objectives: To compare the effects of addition of montelukast or salmeterol to inhaled corticosteroids (ICS) on the response to rescue beta2-agonist use after exercise-induced bronchoconstriction.

Methods: A double-blind, placebo-controlled study was performed at 16 centers in the United States. Patients with asthma (n = 122, ages 15–58) whose symptoms were uncontrolled on low-dose inhaled fluticasone and who had a history of exercise-induced worsening of asthma were randomized to receive either montelukast (10 mg once daily), salmeterol (50 μg twice daily), or placebo for 4 weeks. Standardized spirometry after exercise challenge and beta2-agonist rescue was performed at baseline, week 1 and 4.

Results: Maximum achievable forced expiratory volume in 1 s (FEV1) percent predicted after rescue beta2-agonist improved in the montelukast (+1.5%) and placebo (+1.2%) groups at 4 weeks, but diminished in the salmeterol (−3.9%) group (P<0.001). Although pre-exercise FEV1 was greatest with salmeterol (P=0.10), patients taking montelukast had significantly greater protection from an exercise-induced decrease in FEV1 than those taking salmeterol (P<0.001). Both the magnitude and rate of rescue bronchodilation were greater with montelukast compared with salmeterol (P<0.001). Five minutes after rescue beta2-agonist, 92% of patients taking montelukast and 68% of those taking placebo had recovered to pre-exercise levels, whereas only 50% of those taking salmeterol had recovered to pre-exercise levels.

Conclusion: In patients whose asthma symptoms remain uncontrolled using ICS, addition of montelukast permits a greater and more rapid rescue bronchodilation.
with a short-acting beta2-agonist than addition of salmeterol and provides consistent and clinically meaningful protection against exercise-induced bronchoconstriction.

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Introduction

When asthma control is incomplete on low doses of inhaled corticosteroids (ICS), increasing the dose results in only marginal improvement in efficacy and may increase side effects.1-3 Current guidelines recommend optimizing asthma control by adding another class of therapy, such as the long-acting beta2-agonists (LABA) or leukotriene receptor antagonists (LTRA), to ICS.4,5 Even when asthma symptoms are controlled, episodic worsening may occur after exposure to various asthma-specific triggers, such as exercise, allergen, and cold dry air. These episodes are often treated with short-acting beta2-agonist (SABA) rescue therapy. An add-on therapy to ICS that provides sustained bronchoprotection and permits a robust response to the bronchodilating effects of rescue medication, when needed, would fulfill an important medical need.

Both montelukast, an orally active, selective cysteinyl LTRA, and salmeterol, a LABA, have demonstrated efficacy in adults with persistent asthma. Bronchoprotection with montelukast is present at 1 h6 and persists at the end of the dosing interval without the development of tolerance during 12 weeks of treatment.7 Although salmeterol provides significant initial bronchoprotection against a variety of direct and indirect stimuli, the magnitude of protection decreases with chronic use. Loss of bronchoprotection may begin within a few days to 1 week of treatment with a LABA.8,9 In addition, chronic administration of salmeterol may diminish the acute bronchodilating effect of a SABA.10-14

The current study was designed to compare the effects of 4 weeks of treatment with montelukast with that of salmeterol on the responsiveness after exercise challenge to rescue bronchodilatation with a SABA in asthma patients already receiving ICS. It was hypothesized that montelukast would permit a better rescue bronchodilatation response to beta2-agonist administered after an exercise challenge-induced exacerbation and would demonstrate an advantage in protecting against exercise-induced bronchoconstriction (EIB) when compared with salmeterol.

Methods

Study design

This was a multicenter, randomized, parallel-group, double-blind study consisting of a 2-week, double-placebo period (baseline period) and a 4-week treatment period. A placebo group was included in the treatment period to demonstrate that both active treatment arms produced improvements in the outcomes measured. The study was conducted at 16 centers in the United States. The protocol was approved by a central institutional review board, and written informed consent was obtained from each patient before completing any study procedures. Exercise challenge–rescue procedures were completed at baseline, week 1 and 4.

Inclusion and exclusion criteria

Asthma patients aged between 15 and 45 years old, with at least a 1-year history of asthma currently uncontrolled on ICS for at least 2 months, were enrolled. Asthma treatment at the time of randomization included only SABA and ICS. Patients were eligible for randomization if they had documentation of EIB within the past year showing a decrease in forced expiratory volume in 1 s (FEV1) of at least 15% while receiving ICS (or 20% while not on ICS), an FEV1 of at least 70% of the predicted value at rest, and at least a 12% increase in FEV1 after beta2-agonist administration (demonstrated once during the baseline period). All patients were required to have needed beta2-agonist for more than 3 days per week during the baseline period for treatment of symptoms, indicating the need for additional therapy. Patients with either recent upper respiratory infection (within 3 weeks) or emergency care or hospitalization for asthma within the past 3 months were excluded. Systemic corticosteroids were not allowed for 1 month before the first study visit and throughout the study. With the exception of ICS, patients were required to stop other anti-asthma therapy 2 weeks before the first study visit. Inhaled beta2-agonist for symptomatic relief of
asthma and short-acting antihistamines were permitted. Patients who needed oral corticosteroid treatment or any additional treatment for asthma symptoms were discontinued from the study.

**Study treatment**

All patients received open-label fluticasone (1 inhalation of dry powder inhaler 100 μg twice daily) during the baseline period and continued this treatment for the duration of the study. Eligible patients were randomly assigned, according to a blinded computer-generated allocation schedule, to receive either montelukast sodium (10-mg tablet once daily in the evening), salmeterol xinafoate (50-μg aerosol inhalation twice daily), or placebo. Each patient took one tablet daily (active or matching placebo) and one inhalation twice daily (active or matching placebo) for both the baseline (placebo tablet and placebo inhaler) and treatment periods.

**Evaluations**

Challenge–rescue procedures were completed at baseline, week 1 and 4. Patients were instructed to take an evening dose of study tablet (15–17 h previous) and a morning dose of study inhaler (3–5 h previous) before the procedure. Patients exercised for 6 min on a treadmill, while inhaling room-temperature dry air through a face mask, at a workload that increased heart rate to 80% to 90% of the individual’s age-predicted maximum. The workload required to achieve this target heart rate was used in all procedures.

Pre-exercise spirometry was performed before each challenge–rescue procedure. Pre-exercise FEV₁ (mean of the FEV₁ values at 20 and 5 min before exercise) had to be ≥70% of the predicted value for the procedure to be performed. Serial spirometry was measured immediately after exercise and then at 5, 10, and 15 min. Beta2-agonist rescue (2 puffs of albuterol, 180 μg total) was administered, and serial spirometry was performed 5, 10, 15, and 30 min later. A second beta2-agonist rescue (2 puffs of albuterol, 180 μg total) was administered, and spirometry was performed again 30 min later. At baseline and week 4, patients completed the clinic exercise-assessment questionnaire (CEAQ) to describe the degree of their symptoms immediately after exercise, 10 min after exercise, and 10 min after the first administration of rescue beta2-agonist. The CEAQ was administered by the study coordinator and consisted of questions about shortness of breath, wheezing, and chest tightness graded on a 7-point scale. Additional beta2-agonist rescue was permitted outside of the protocol-required timepoints for distressing symptoms at the discretion of the investigator, but remaining spirometry maneuvers in those sets were not completed.

Spirometry was performed according to American Thoracic Society acceptability and reproducibility criteria using a standard spirometer (KoKo Spirometer, PDS Instrumentation, Louisville, CO). Patients were required to withhold the use of inhaled beta2-agonist for at least 6 h before the visit. All spontaneously reported adverse experiences were recorded at each visit during the double-blind period.

Based on the serial spirometry measurements of FEV₁, the pre-exercise level, minimum level after exercise, and maximum level after rescue beta2-agonist were determined. Exercise-induced exacerbation of asthma was defined as the percentage difference between average pre-exercise and minimum postexercise FEV₁ values. Rescue bronchodilation was defined as the percentage difference between average pre-exercise and maximum post-rescue beta2-agonist FEV₁ values. The time-to-recovery to pre-exercise FEV₁ was defined as the time needed to reach pre-exercise levels of FEV₁.

**Figure 1** Challenge–rescue procedure endpoints. The pre-exercise, postexercise minimum, postrescue beta2-agonist 1 and 2 maximum FEV₁ percent predicted time points on the graph are each connected with the corresponding portion of the stacked bar by the dashed arrows. The stacked bar graphs show exercise-induced exacerbation (solid bar) and rescue bronchodilation after the first (open bar) and second (hashed bar) beta2-agonist administrations for each visit, as indicated. EX = exercise; RA1 = first rescue albuterol administration, 15 min after completion of exercise; RA2 = second rescue albuterol administration, 30 min after first rescue beta2-agonist administration; *primary endpoint.
after first beta2-agonist rescue was administered; see Fig. 1 for an illustration of endpoints.

**Statistical methods**

The primary objective was to determine the effect of 4 weeks of treatment with placebo, montelukast, and salmeterol on maximum FEV$_1$ after beta2-agonist administration. The secondary objectives were to determine the effect of treatments on pre-exercise FEV$_1$, exercise exacerbation, rescue bronchodilation, time-to-recovery to pre-exercise FEV$_1$ level, and average CEAQ score. The frequency of adverse experiences also was evaluated.

For FEV$_1$ variables, an analysis of covariance model, including terms for treatment and baseline covariates, was used to estimate the difference between treatment groups for each endpoint. A modified intention-to-treat approach was used for efficacy analyses. For FEV$_1$, all randomized patients who had challenge–rescue evaluations at baseline and during treatment were eligible for analyses. There was no imputation of missing values, and prior values were not carried forward. Time-to-recovery of FEV$_1$ was analyzed using Kaplan–Meier time-to-event estimates with corresponding Wilcoxon statistics. Recovery time was estimated by linear interpolation of the two timepoints on either side of the pre-exercise FEV$_1$ percent predicted value. Analysis of covariance was used to compare the change from baseline to week 4 for the 0- and 10-min postexercise timepoints and the 10-minute postrescue timepoint of the CEAQ. Descriptive statistics were computed by treatment group for patient demographics and clinical characteristics. All statistical analyses were performed using SAS$^{10}$ Version 6 (SAS Institute, Inc., Cary, NC).

**Results**

**Patients**

Figure 2 shows the disposition of patients in this study. The most common reason for disqualification was failure to meet a 15% decrease in FEV$_1$ with exercise. A total of 119 patients (97.5%) completed the 4-week, double-blind study; three patients discontinued prematurely for the reason indicated in Fig. 2. More women and fewer men were enrolled in the montelukast group than in the salmeterol or placebo groups, although this difference was not statistically significant. All other demographic and baseline clinical characteristics were comparable among the three treatment groups (Table 1).

Nine patients (three from each treatment group) were enrolled at a site noted to have irregularities with Good Clinical Practice after the study was completed. All analyses were performed both with and without data from these nine patients, and there were no meaningful differences between the analyses. The results presented exclude data from these nine patients.

**Challenge-rescue**

FEV$_1$ values expressed as percent predicted before and during the challenge–rescue procedures and the degree of EIB and rescue bronchodilation at baseline, week 1 and 4 are shown in Fig. 3 and Table 2. At baseline, the three treatment groups had comparable pre-exercise, minimum postexercise, and maximum postalbuterol FEV$_1$ values.

Maximum FEV$_1$ after first beta2-agonist rescue

After 4 weeks of therapy, maximum postalbuterol rescue FEV$_1$ percent predicted values improved in the montelukast and placebo treatment groups, but diminished in the salmeterol group (+1.5%, +1.2%, and −3.9% for montelukast, placebo, and salmeterol, respectively; Table 2). The maximum FEV$_1$ in the salmeterol group was significantly less than the maximum FEV$_1$ in both the montelukast ($P<0.001$) and placebo ($P<0.001$) groups. Results
obtained after 1 week of therapy had similar values of $+1.7\%$, $+1.7\%$, and $-3.1\%$ for montelukast, placebo, and salmeterol, respectively. The treatment effects observed between montelukast and placebo were not significantly different. The maximum FEV$_1$ values obtained after the second beta2-agonist rescue (Table 2) are consistent with those seen after the first rescue.

**Pre-exercise FEV$_1$**
There were small increases compared with baseline values in pre-exercise FEV$_1$ percent predicted for salmeterol-treated patients at weeks 1 and 4, but not in patients receiving either montelukast or placebo (Table 2). The mean change from baseline in pre-exercise FEV$_1$ percent predicted was significantly greater in the salmeterol treatment group compared to the montelukast treatment group at weeks 1 and 4 ($P = 0.010$) and to the placebo group at week 1 ($P < 0.001$). There was no significant difference between montelukast and placebo treatment groups with respect to pre-exercise FEV$_1$ percent predicted values.

**Exercise-induced exacerbation**
Mean baseline measures of EIB were generally comparable among the montelukast, salmeterol, and placebo groups (Table 2). The improvement from baseline to week 4 was $-5.5\%$, $-3.1\%$, and $-0.5\%$, respectively. Compared with placebo, montelukast significantly decreased EIB at week 4 ($P = 0.008$). The treatment effects observed between salmeterol and placebo and between salmeterol and montelukast were not significantly different. At week 1, the change from baseline in EIB was $-6.4\%$, $-1.2\%$, and $-0.6\%$ for the montelukast, salmeterol, and placebo groups, respectively. The improvement with montelukast was significantly greater than that with either salmeterol ($P = 0.004$) or placebo ($P < 0.001$). The treatment effect observed between salmeterol and placebo at week 1 was not significantly different.

**Rescue bronchodilation**
Mean baseline measures of rescue bronchodilation were generally comparable among the montelukast, salmeterol, and placebo groups after the first and second beta2-agonist rescues (Table 2). The mean changes from baseline to week 4 in rescue bronchodilation after the first beta2-agonist rescue were $+1.6\%$, $-7.9\%$, and $-0.3\%$ for the montelukast, salmeterol, and placebo treatment groups, respectively. The loss in rescue bronchodilation seen with salmeterol was significant compared with montelukast and placebo ($P < 0.001$). The treatment effects observed between montelukast and placebo were not significantly different. The analyses of rescue bronchodilation after the second beta2-agonist rescue were consistent with those observed after rescue 1. Similarly, the results obtained at week 1 were consistent with those obtained at week 4.

**Time-to-recovery**
After 4 weeks of therapy, montelukast permitted significantly faster rescue with beta2-agonist compared with both salmeterol ($P = 0.005$) and placebo ($P = 0.036$; Fig. 4). Patients treated with salmeterol had slower beta2-agonist rescue response compared with those taking placebo, although the

<table>
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<th>Table 1 Demographic and Baseline Clinical Characteristics.</th>
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<td>Montelukast/ fluticasone</td>
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<tr>
<td>(n = 39)</td>
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<tr>
<td>Age (years), mean (range)</td>
</tr>
<tr>
<td>Men (%)</td>
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<tr>
<td>Women (%)</td>
</tr>
<tr>
<td>Caucasian (%)</td>
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<tr>
<td>Black (%)</td>
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<tr>
<td>Hispanic (%)</td>
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<tr>
<td>Asthma duration (years), mean $\pm$ SD</td>
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<td>Pre-exercise FEV$_1$ (L), mean $\pm$ SD</td>
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<tr>
<td>Pre-exercise FEV$_1$ (% predicted), mean $\pm$ SD</td>
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<tr>
<td>Maximum % decrease in FEV$_1$</td>
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<td>Reversibility (% $\pm$ SD)</td>
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<tr>
<td>Total beta2-agonist use (puffs/day) $\pm$ SD</td>
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difference was not significant. At week 4, 92%, 50%, and 68% of patients in the montelukast, salmeterol, and placebo groups, respectively, recovered to pre-exercise FEV₁ levels 5 min after rescue with beta2-agonist. By 30 min postrescue, the percentages were 100%, 71%, and 89% of patients in the

Figure 3 FEV₁ during the challenge-rescue procedure. Graphs show the mean FEV₁ percent predicted and standard error after exercise challenge and beta2-agonist rescue at baseline (solid circle, solid line), week 1 (solid triangle, dashed line), and week 4 (open square, solid line). The corresponding stacked bar graphs show exercise-induced exacerbation (solid bar), rescue bronchodilation after the first (open bar), and second (hashed bar) beta2-agonist administrations for each visit, as indicated below each bar. Change from baseline analyses: ²P < 0.010 versus montelukast and placebo at week 1 and 4; ¹P < 0.01 versus montelukast at week 4.
<table>
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<th>Table 2</th>
<th>Challenge-rescue efficacy values.</th>
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<td>Montelukast/fluticasone</td>
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<td></td>
<td>Baseline (n = 36)</td>
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<td>Maximum FEV₁ (% predicted) after first beta2-agonist rescue, mean (SD)</td>
<td>94.7 (11.3)</td>
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<tr>
<td>Maximum FEV₁ (% predicted) after second beta2-agonist rescue, mean (SD)</td>
<td>96.0 (11.5)</td>
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<tr>
<td>Pre-exercise FEV₁ (% predicted), mean (SD)</td>
<td>86.9 (10.3)</td>
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<tr>
<td>Exercise-induced exacerbation (maximum percent fall from pre-exercise FEV₁), mean (SD)</td>
<td>12.9 (11.3)</td>
</tr>
<tr>
<td>Rescue bronchodilation (maximum percent rise from pre-exercise FEV₁ after first beta2-agonist rescue), mean (SD)</td>
<td>9.2 (7.2)</td>
</tr>
<tr>
<td>Rescue bronchodilation (maximum percent rise from pre-exercise FEV₁ after second beta2-agonist rescue), mean (SD)</td>
<td>10.7 (7.8)</td>
</tr>
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</table>
montelukast, salmeterol, and placebo groups, respectively. Similar results were observed after 1 week of therapy.

**Clinic exercise-assessment questionnaire**

At baseline, all patients noted the highest degree of symptoms immediately after exercise and showed an improvement in CEAQ score 10 min later, with further improvement after rescue beta2-agonist administration. After 4 weeks of treatment, significant differences in the mean CEAQ score immediately after exercise and 10 min after exercise (Fig. 5) were found between patients in the montelukast and placebo groups ($P < 0.020$). In addition, patients treated with placebo had a marked improvement in their symptoms after beta2-agonist rescue, unlike the patients in the salmeterol group.

**Safety**

Both montelukast and salmeterol were generally well tolerated. There were no serious clinical adverse experiences. One patient treated with salmeterol discontinued because of a clinical adverse event (intervertebral disc displacement). No patients experienced an asthma attack during the study.

**Discussion**

Guidelines for the treatment of persistent asthma recommend that daily controller therapy with ICS and additional agents, if needed, be used to minimize the impact of the disease. These guidelines further recommend that SABA therapy be available "as needed" to treat exacerbations.$^{4,5}$
The current study demonstrated that patients treated with montelukast had significantly greater response to beta2-agonist compared with patients taking salmeterol at 1 and 4 weeks of therapy. This finding was a result of a decrease in the level and rapidity of rescue bronchodilation in patients taking salmeterol. Furthermore, patients receiving montelukast had a significantly greater attenuation of EIB compared with those taking placebo, whereas patients taking salmeterol did not. These differences were present after 1 week of treatment and persisted over 4 weeks, consistent with previous comparisons of montelukast and salmeterol in the attenuation of EIB in patients not receiving ICS. The findings of the current study also confirm previously published reports that chronic administration of LABAs decrease the effects of SABAs in a variety of settings.

Chronic stimulation of beta2-adrenergic receptors is known to cause downregulation of airway smooth muscle receptor numbers and uncoupling of intracellular signaling. This, in turn, results in a decreased sensitivity of the beta2-adrenergic receptor to further stimulation by the agonist, including a SABA. Tachyphylaxis may occur even in the presence of concomitantly administered ICS. In addition, salmeterol is known to be a partial agonist with a long receptor occupancy time, which could have prevented beta2-agonist access to the receptors. Because the beta2-agonist rescue was performed at the time of peak salmeterol concentration during chronic dosing, both of these phenomena probably contributed to the decrease in response to beta2-agonist rescue in the current study.

In contrast, montelukast has no known effect on the function of beta2 receptors. Previous studies have consistently shown an additive bronchodilating effect of beta2-agonist in patients treated with montelukast, suggesting that airway smooth muscle tone is maintained by both leukotriene and adrenergic stimulation. Thus, the preservation of full bronchodilator effect with beta2-agonist in patients treated with montelukast is not surprising.

Although the patients in this study had moderate asthma, they had relatively mild exercise-induced worsening of airflow at baseline, despite a history of at least a 15% decrease in FEV1 in the previous year. The differences between the postrescue beta2-agonist maximum FEV1 values among the treatment groups, although statistically significant, were small. Despite these small differences in airway function, patients perceived differences in postexercise symptoms, as demonstrated by the CEAQ responses, 10 min before and 10 min after rescue beta2-agonist was given, suggesting that these differences are clinically important. Patients’ perceptions of impairment from EIB exacerbations may be affected by the duration of the exacerbation. Approximately 20% of patients treated with salmeterol failed to return to their pre-exacerbation baseline status 30 min after rescue beta2-agonist administration. Thus, the significantly slower bronchodilator response noted in patients on salmeterol may have contributed to their perceptions. In addition, patients may be better able to perceive changes (i.e., improvements) rather than absolute levels in their airway function.

Salmeterol demonstrated a pre-exercise bronchodilation effect that persisted during the 4 weeks of treatment, consistent with previous findings. However, the level of maximum FEV1 achieved with salmeterol was less than that seen with beta2-agonist at baseline. After 1 week of salmeterol therapy, patients were unable to obtain the maximal bronchodilator response to beta2-agonist that was observed before salmeterol therapy. Previous studies comparing salmeterol and montelukast as add-on therapy to ICS have not evaluated responsiveness to rescue beta2-agonist as an endpoint. Nelson and colleagues examined both agents added to inhaled fluticasone for 12 weeks and found that salmeterol provided greater improvement in peak expiratory flow and reduction in the frequency of rescue beta2-agonist use; however, they did not measure airflow during exacerbations or after rescue treatment. Rescue bronchodilation after methacholine-induced exacerbation has been investigated in patients receiving salmeterol or formoterol. van der Woude and colleagues found that after 4 weeks of treatment, patients who had taken either drug had significantly less and slower rescue bronchodilation compared with those treated with placebo, similar to the findings in the current study. Lipworth et al. found that treatment with formoterol led to tachyphylaxis to bronchoprotection against methacholine challenge after 2 weeks of therapy, but the bronchodilator effects were maintained during this period.

Both montelukast and salmeterol were well tolerated in this study. There were no significant between-group differences in the frequency of clinical or laboratory adverse experiences, and no patient experienced an asthma attack during this short study. Montelukast is a potential companion therapy for patients with persistent asthma who are already being treated with ICS. In patients who also have a component of EIB, montelukast may have an advantage over LABA add-on therapy because it can provide persistent attenuation of
the exercise-induced decrease in FEV₁, and it has an additive effect with rescue SABA therapy. Further, this study highlights the importance of evaluating the consequence of chronic asthma therapy on the effect of “as-needed” rescue bronchodilator treatment, an important aspect of asthma care.

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