Effect of montelukast or salmeterol added to inhaled fluticasone on exercise-induced bronchoconstriction in children

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Objectives: To evaluate the effect of montelukast, 5 mg, or inhaled salmeterol, 50 μg, added to inhaled fluticasone in reducing the maximum percentage decrease in forced expiratory volume in 1 second (FEV₁) after a standardized exercise challenge and response to rescue bronchodilation with albuterol in children aged 6 to 14 years with persistent asthma and exercise-induced bronchoconstriction (EIB).

Methods: Randomized, double-blind, double-dummy, multicenter, 2-period, 4-week, crossover study conducted between December 22, 2005 and November 14, 2008 at 30 centers in Europe, Asia, Mexico, and South America. Patients with asthma receiving inhaled corticosteroids demonstrated an FEV₁ of 70% or higher of the predicted value and EIB (defined as a decrease in FEV₁ ≥15% compared with preexercise baseline FEV₁ on 2 occasions before randomization). Standardized exercise challenges were performed at baseline (prerandomization) and at the end of each active treatment period.

Results: Of 154 patients randomized, 145 completed the study. Montelukast, compared with salmeterol, significantly reduced the mean maximum percentage decrease in FEV₁ (10.6% vs 13.8%; P = .009), mean area under the curve for the first 20 minutes after exercise (116.0%·min vs 168.8%·min; P = .006), and median time to recovery (6.0 vs 11.1 minutes; P = .04). Response to albuterol rescue after exercise challenge was significantly greater (P<.001) with montelukast. Montelukast and salmeterol were generally well tolerated.

Conclusions: Attenuation and response of EIB to albuterol rescue after exercise challenge were significantly better with montelukast than with salmeterol after 4 weeks of treatment.


INTRODUCTION
Periodic exacerbations of persistent asthma commonly follow exposures to specific triggers, such as exercise, allergen, and cold air. Exercise-induced bronchoconstriction (EIB) is a common manifestation of asthma, occurring in 80% to 90% of individuals with asthma.1 EIB is particularly problematic for children, who often participate in unplanned activities, and limits everyday activities important for balanced physical, psychological, and social development.3

Montelukast has been shown to protect against EIB when administered as a single dose 1 to 2 hours before exercise4–7 and at the end of the dosing interval (ie, 20-24 hours after dosing) when administered for 2 days8,9 or on a daily basis for as long as 12 weeks.10,11 In studies comparing montelukast and salmeterol, a long-acting β-agonist (LABA), similar protection against EIB was seen after single-dose administration. Tolerance, however, has been observed with long-term use of salmeterol, with or without concomitant inhaled corticosteroids, but not with long-term use of montelukast.10,11 In addition, long-term salmeterol use has been associated with diminished response to short-acting β-agonist (SABA) rescue after exercise challenge. This has not been observed with montelukast.13 We conducted a study comparing the effect of 4 weeks of montelukast or salmeterol added to inhaled fluticasone in 6- to 14-year-olds with persistent asthma and EIB, evaluating both the protection against EIB and the response to SABA rescue after exercise challenge.

METHODS
This study (Merck protocol 911) was a multicenter, double-blind, double-dummy, randomized, crossover study that consisted of a 4-week baseline run-in period and two 4-week active treatment periods separated by a 2-week washout period. The study was conducted between December 22, 2005
and November 14, 2008 at 30 centers in Europe, Asia, Mexico, and South America. The protocol was approved by ethical review committees of all participating study centers; written informed consent was obtained from each patient’s parent or legal guardian and informed assent from each patient before any study procedures were performed.

**Patients**

Boys and girls between 6 and 14 years of age with at least a 1-year clinical history of asthma and who were using daily inhaled corticosteroids for at least 8 weeks before participating in the study were eligible. Patients were eligible for randomization after demonstrating, while taking open-label fluticasone, a forced expiratory volume in 1 second (FEV₁) of 70% or more of the predicted value (at each visit during the baseline period) and EIB, defined as a decrease in FEV₁ of at least 15% compared with preexercise baseline FEV₁ (twice during the baseline period). Exclusion criteria included the following: unresolved signs and symptoms of an upper respiratory tract infection within 1 week; evidence of active, clinically significant sinus infection; history of intubation for asthma; short-term asthma therapy in an emergency department, urgent care facility, or office setting within 1 month or hospitalization for asthma within 3 months; oral, intravenous, rectal, intramuscular, or intra-articular corticosteroids within 1 month; cromolyn, nedocromil, or leukotriene receptor antagonists within 1 week, theophylline within 1 week, or oral β-agonists or LABAs within 1 week; or astemizole within 3 months before the first study visit. Use of nasal corticosteroids or nasal cromolyn for allergic rhinitis and continuation of immunotherapy (initiated at least 6 months before the first study visit) were allowed for patients taking stable doses at baseline. SABAs (salbutamol or albuterol) were permitted on an as-needed basis for rescue; if oral corticosteroids or other treatment for asthma was required, the patient was discontinued from the study.

**Study Design**

All patients received open-label fluticasone, 50 μg, 2 puffs twice daily, throughout the study (baseline, active treatment, and washout periods). After a 4-week placebo run-in, eligible patients were randomly assigned, according to a computer-generated allocation schedule, to 1 of 2 treatment sequences: montelukast and placebo-matching salmeterol or salmeterol and placebo-matching montelukast. After a 2-week washout, patients crossed over to the other treatment. Montelukast, 5 mg, and matching-image chewable placebo tablets were administered nightly at bedtime; salmeterol, 50 μg, and matching-image placebo inhalers were administered in the morning and in the evening. SABAs were withheld for at least 6 hours before each visit.

Numbered inhalers and bottles were used to implement allocation. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel, remained masked to treatment allocation throughout the study. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete. As a further quality control measure after unmasking, the data in the study reports and manuscript were verified for accuracy against the database.

Exercise challenges were performed, consistent with American Thoracic Society guidelines, during the baseline run-in period and at the end of each 4-week treatment period. For each patient, all exercise challenges were performed 8 to 10 hours after the morning dose and 20 to 24 hours after the evening dose of study drug, near the trough of effect for salmeterol and montelukast, respectively. Patients exercised for at least 6 minutes on the treadmill, while inhaling room-temperature dry air (from a compressed-air tank), at a workload that increased the heart rate to 50% to 70% of the individual’s age-predicted maximum (220 – age [years]) during the first 2 minutes and to 80% to 90% of the age-predicted maximum thereafter. During the first exercise challenge in the run-in period, treadmill speed and incline were adjusted to determine the appropriate conditions that allowed the heart rate to be maintained at 80% to 90% of the individual’s age-predicted maximum for 6 minutes. This workload was then used for all subsequent challenges, although small adjustments in workload were allowed to achieve the targeted heart rate.

Baseline spirometry was performed 20 and 5 minutes before exercise challenges. FEV₁ (average of the 20- and 5-minute values) had to be at least 70% of the predicted value to proceed with the exercise challenge. The largest FEV₁ from the acceptable and reproducible maneuvers at a time point was considered the true value for that time point.

FEV₁ was measured immediately after the exercise challenge and at 5, 10, 15, and 20 minutes after the challenge. All patients received inhaled SABA (200 μg) after the 20-minute postchallenge measurement. FEV₁ was then measured 5, 10, 15, and 30 minutes after the first SABA administration. All challenges were performed, consistent with American Thoracic Society guidelines, during the baseline run-in period and at the end of each 4-week treatment period. For each patient, all exercise challenges were performed 8 to 10 hours after the morning dose and 20 to 24 hours after the evening dose of study drug, near the trough of effect for salmeterol and montelukast, respectively. Patients exercised for at least 6 minutes on the treadmill, while inhaling room-temperature dry air (from a compressed-air tank), at a workload that increased the heart rate to 50% to 70% of the individual’s age-predicted maximum (220 – age [years]) during the first 2 minutes and to 80% to 90% of the age-predicted maximum thereafter. During the first exercise challenge in the run-in period, treadmill speed and incline were adjusted to determine the appropriate conditions that allowed the heart rate to be maintained at 80% to 90% of the individual’s age-predicted maximum for 6 minutes. This workload was then used for all subsequent challenges, although small adjustments in workload were allowed to achieve the targeted heart rate.

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FEV₁ was measured immediately after the exercise challenge and at 5, 10, 15, and 20 minutes after the challenge. All patients received inhaled SABA (200 μg) after the 20-minute postchallenge measurement. FEV₁ was then measured 5, 10, 15, and 30 minutes after the first SABA administration. All
patients received a second planned SABA administration (200 μg) after the 30-minute measurement; the final FEV₁ measurement was performed 30 minutes after the second planned SABA administration. Additional inhaled or nebulized SABA was permitted as needed.

Efficacy and Safety End Points

The primary end point was the maximum percentage decrease in FEV₁ after exercise and before SABA administration (Figure 1). Key secondary end points included the area under the curve for the first 20 minutes after exercise (AUC0–20min), time to recovery within 5% of preexercise FEV₁, maximum FEV₁ percentage predicted after SABA administration, and average percentage change from preexercise baseline in FEV₁ after SABA administration.

Exploratory end points included the categorical maximum percentage decrease in FEV₁ (<10%, ≥10 to ≤20%, or >20%) after exercise and before SABA use; maximum percentage change in FEV₁ after the first administration of a SABA (planned or rescue); average percentage change from preexercise baseline in FEV₁ after second administration of a SABA and after both first and second SABA uses; and the need for rescue (ie, unplanned) medication during and after exercise challenge. Safety was assessed by the incidence of clinical adverse experiences (AEs), serious AEs, drug-related AEs, and AEs resulting in discontinuation.

Statistical Analyses

Efficacy analyses included all randomized patients who took at least 1 dose of study drug and had spirometry measurements for analysis in both treatment periods (full analysis set population). The primary efficacy variable of interest was the maximum percentage decrease in FEV₁ after exercise and before SABA administration. Data were analyzed using an analysis of variance (ANOVA) model with factors for patient, treatment, and period effect. There was 1 primary hypothesis, assessed with 1 variable (maximum percentage decrease in FEV₁ after exercise), 1 between-group comparison (montelukast vs salmeterol), and 1 time point (after 4 weeks of study therapy). Therefore, no multiplicity adjustment for the primary analysis was needed. An analysis of the per-protocol population was also performed for the maximum percentage decrease in FEV₁ after exercise.
The secondary efficacy variables, the AUC[0–20] and time-weighted average percentage change in FEV1, were analyzed using a similar parametric ANOVA model as described herein for the primary efficacy variable. If rescue SABA therapy was administered before 20 minutes, the last FEV1 value for the patient was carried forward. The maximum FEV1 percentage predicted and maximum percentage change after SABA administration was analyzed using an analysis of covariance model with factors for patient, treatment, and period and a covariate for FEV1 percentage predicted at preexercise baseline. Time to recovery was analyzed using a Cox proportional hazard model with factors for treatment and period. If FEV1 did not decrease below 95% of the baseline level, the time to recovery was assigned a value of zero. In the case where FEV1 did not recover to within 5% of the preexercise baseline or if the patient needed a second administration of SABA (planned or rescue) before recovery, then the observation was censored at the last valid spirometry measurement before the second administration of SABA. The number and percentage of patients requiring rescue (ie, unplanned) medication were summarized by treatment. The categorical maximal percentage decrease in FEV1 (<10%, ≥10% to ≤20%, or >20% of preexercise baseline) was analyzed using the Cochran Q for the proportion of patients in each category. The study was designed to have 85% power (α = .05) to demonstrate a difference of 2.4% in the maximum percentage decrease in FEV1, assuming an SD of 0.3 and 155 patients.

Safety analyses included randomized patients who received at least 1 dose of study therapy and were assessed based on the Wilson score. The AEs that occurred during the washout between treatment periods were attributed to the active treatment last received.

RESULTS

Patients and Baseline Characteristics

A total of 401 patients were screened, of whom 154 were randomized and 145 completed the study (Figure 2). Of the 247 patients who did not qualify for randomization, 186 (75.3%) failed to fulfill spirometry criteria (FEV1 ≥70% of the predicted value on 3 occasions) and/or exercise challenge criteria (a decrease in FEV1 of at least 15% compared with preexercise baseline FEV1 on 2 occasions). A total of 144 patients comprised the full analysis data set for evaluation of efficacy; 150 patients who received montelukast and 150 patients who received salmeterol were included in safety analyses.

Baseline patient demographic characteristics are presented in Table 1. The treatment sequences were generally comparable at baseline. Most patients were white and male; the mean age of the patient cohort was 10 years.

Efficacy

Montelukast was significantly better than salmeterol (mean, 10.6% vs 13.8%; P = .009) for the primary end point of maximum percentage decrease in FEV1 (Table 2) and for mean percentage change in FEV1 after exercise (Figure 3). Results from a per-protocol approach for maximum percentage decrease in FEV1 were consistent (mean, 9.49% vs 12.78%; P = .02) with those from the full analysis set population. Montelukast also provided significantly more effective bronchoprotection than salmeterol as shown by a smaller AUC[0–20] (P = .006) and a shorter time to recovery (P = .04). The response to SABA administration after exercise challenge was significantly (P<.001) greater with montelukast than with salmeterol, as shown by maximum FEV1 percentage predicted after the first SABA use (mean, 103.1% vs 100.9%) and average percentage change in FEV1 after the first SABA use (mean, 6.5% vs 2.7%), after the second SABA use (mean, 8.4% vs 5.1%), and after both SABA uses (mean, 7.5% vs 3.9%). No treatment period effect was observed (ie, there was no difference in response based on order of treatment received).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Montelukast (n = 78)</th>
<th>Salmeterol-montelukast (n = 76)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>43 (55.1)</td>
<td>46 (60.5)</td>
</tr>
<tr>
<td>Female</td>
<td>35 (44.9)</td>
<td>30 (39.5)</td>
</tr>
<tr>
<td>Race, No. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (1.3)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Black</td>
<td>11 (14.1)</td>
<td>7 (9.2)</td>
</tr>
<tr>
<td>White</td>
<td>38 (48.7)</td>
<td>41 (53.9)</td>
</tr>
<tr>
<td>Other</td>
<td>28 (35.9)</td>
<td>28 (36.8)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>10.2 (2.0)</td>
<td>9.8 (2.0)</td>
</tr>
<tr>
<td>Preexercise FEV1, mean (SD), L</td>
<td>2.30 (1.1)</td>
<td>2.2 (0.6)</td>
</tr>
<tr>
<td>Preexercise FEV1, mean (SD), % predicted</td>
<td>96.3 (31.8)</td>
<td>92.8 (12.4)</td>
</tr>
<tr>
<td>Maximum percentage decrease in FEV1, after exercise, mean (SD)</td>
<td>24.8 (10.3)</td>
<td>25.4 (9.0)</td>
</tr>
<tr>
<td>AUC[0–20min], mean (SD), %·min</td>
<td>320.1 (208.6)</td>
<td>317.7 (165.7)</td>
</tr>
<tr>
<td>Time to recovery, mean (SD), min</td>
<td>23.5 (10.5)</td>
<td>21.5 (8.3)</td>
</tr>
<tr>
<td>Maximum FEV1, mean (SD), % predicted</td>
<td>99.9 (32.5)</td>
<td>100.5 (15.6)</td>
</tr>
<tr>
<td>Average percentage change in FEV1, after first SABA use, mean (SD)</td>
<td>1.4 (11.0)</td>
<td>4.8 (10.9)</td>
</tr>
<tr>
<td>Need for rescue medication after challenge, No. (%)</td>
<td>77 (98.7)</td>
<td>75 (98.7)</td>
</tr>
<tr>
<td>No</td>
<td>1 (1.3)</td>
<td>1 (1.3)</td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma exacerbations limited normal physical activity, No. (%)</td>
<td>2 (2.6)</td>
<td>4 (5.3)</td>
</tr>
<tr>
<td>Not at all</td>
<td>21 (26.9)</td>
<td>20 (26.3)</td>
</tr>
<tr>
<td>Slightly</td>
<td>46 (59.0)</td>
<td>44 (57.9)</td>
</tr>
<tr>
<td>Moderately</td>
<td>9 (11.5)</td>
<td>8 (10.5)</td>
</tr>
</tbody>
</table>

Abbreviations: AUC[0–20], area under the curve for the first 20 minutes after exercise; FEV1, forced expiratory volume in 1 second; SABA, short-acting β-agonist.

a Based on the number of patients who returned to within 5% of the baseline FEV1 value.
In a prespecified exploratory analysis, patients were categorized based on their maximum percentage decrease in FEV₁ (≤10%, >10 to ≤20%, or >20%) after exercise and before SABA use. Montelukast treatment, compared with salmeterol treatment, resulted in a significant shift of patients toward a lower category decrease (P = .004) (Figure 4), with 63.2% of patients treated with montelukast falling into the less than 10% maximum percentage decrease in FEV₁ category compared with 44.4% of patients treated with salmeterol. Two patients, both in the salmeterol-montelukast sequence, needed rescue medication after exercise challenge: one patient was rescued after salmeterol treatment and the other was rescued after montelukast treatment.

Safety
Both montelukast and salmeterol were generally well tolerated in this study. No significant between-treatment differ-

### Table 2. Exercise Challenge End Points Measured After 4 Weeks of Treatment

<table>
<thead>
<tr>
<th>End Point</th>
<th>Montelukast (n = 144)</th>
<th>Salmeterol (n = 144)</th>
<th>Difference in LS mean (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum percentage decrease in FEV₁, mean (SD)</td>
<td>10.6 (12.2)</td>
<td>13.8 (12.5)</td>
<td>-3.3 (-5.7 to -0.8)</td>
<td>.009</td>
</tr>
<tr>
<td>Secondary end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC_{20min}, mean (SD), %·min</td>
<td>116.0 (187.5)</td>
<td>168.8 (199.6)</td>
<td>-52.7 (-89.8 to -15.7)</td>
<td>.006</td>
</tr>
<tr>
<td>Time to recovery to within 5% of baseline FEV₁, median, min</td>
<td>5.9</td>
<td>11.1</td>
<td>1.3 (1.0 to 1.6)</td>
<td>.04</td>
</tr>
<tr>
<td>Maximum FEV₁ percentage predicted after first SABA use, mean (SD)</td>
<td>103.1 (15.8)</td>
<td>100.9 (13.4)</td>
<td>4.1 (2.6 to 5.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Average percentage change in FEV₁ after first SABA use, mean (SD)</td>
<td>6.5 (8.8)</td>
<td>2.7 (6.1)</td>
<td>3.8 (2.3 to 5.3)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Exploratory end points</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum percentage change in FEV₁ after first SABA use, mean (SD)</td>
<td>9.8 (9.4)</td>
<td>5.3 (6.4)</td>
<td>4.3 (2.6 to 5.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Average percentage change in FEV₁ after second SABA use, mean (SD)</td>
<td>8.4 (9.3)</td>
<td>5.1 (7.5)</td>
<td>3.3 (1.5 to 5.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Average percentage change in FEV₁ after both SABA uses, mean (SD)</td>
<td>7.5 (8.2)</td>
<td>3.9 (6.1)</td>
<td>3.5 (2.1 to 5.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Patients requiring rescue medication after exercise challenge, No. (%)</td>
<td>1 (0.7)</td>
<td>0 (0.0)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: AUC, area under the curve; CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LS, least squares; SABA, short-acting β-agonist.

a Number of patients with measurements in both treatment periods.
b Based on analysis of variance model with factors for patient, treatment, and period effects.
c Analysis limited to number of patients (n = 141 for the montelukast group and n = 142 for the salmeterol group) who returned to within 5% of the baseline FEV₁ value.
d Hazard ratio (95% CI) based on Cox proportional hazards model with factors for treatment and period.
e Based on analysis of covariance model with factors for patient, treatment, and period effect and a covariate for FEV₁ percentage predicted at preexercise baseline.

In a prespecified exploratory analysis, patients were categorized based on their maximum percentage decrease in FEV₁ (<10%, ≥10 to <20%, or >20%) after exercise and before SABA use. Montelukast treatment, compared with salmeterol treatment, resulted in a significant shift of patients toward a lower category decrease (P = .004) (Figure 4), with 63.2% of patients treated with montelukast falling into the less than 10% maximum percentage decrease in FEV₁ category compared with 44.4% of patients treated with salmeterol. Two patients, both in the salmeterol-montelukast sequence, needed rescue medication after exercise challenge: one patient was rescued after salmeterol treatment and the other was rescued after montelukast treatment.

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**Figure 3.** Mean percentage change in forced expiratory volume in 1 second (FEV₁) after exercise by time point at prerandomization baseline and after treatment with montelukast and salmeterol (full analysis set). SABA indicates short-acting β-agonist.

**Figure 4.** Categorical analysis of maximum percentage decrease in forced expiratory volume in 1 second (FEV₁) after exercise demonstrated montelukast vs salmeterol was associated with a significant population shift toward greater protection from exercise-induced bronchoconstriction (P = .004; calculated using the Cochran Q for comparison of montelukast vs salmeterol).
Table 3. Incidence of Clinical Adverse Experiences

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Montelukast, No (%)</th>
<th>Salmeterol, No (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>With &gt;1 adverse experiences</td>
<td>28 (18.7)</td>
<td>22 (14.7)</td>
</tr>
<tr>
<td>With drug-related adverse experiences</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>With serious adverse experiences</td>
<td>1 (0.7)</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Discontinued because adverse experiences</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

A patient is counted only once within a category and a treatment; the same patient may appear in different categories.

DISCUSSION

In our crossover study of 6- to 14-year-old children with persistent asthma receiving inhaled fluticasone, 4 weeks of once-daily treatment with montelukast, 5 mg, provided significantly greater bronchoprotection against EIB than 4 weeks of twice-daily treatment with salmeterol, 50 μg, as measured by the end points of maximum percentage decrease in FEV₁, AUC₀⁻²₀, and time to recovery to within 5% of the preexercise value. In addition, response to SABA rescue after exercise challenge was significantly greater with montelukast than with salmeterol. Both montelukast and salmeterol were generally well tolerated in our study.

Our results confirm those of previous exercise challenge studies in children and adults in which montelukast, compared with placebo or LABAs, provided significant and clinically meaningful prevention of EIB after single-dose or long-term administration. In contrast to the effect of LABAs, the ability of montelukast to prevent clinically significant deterioration in FEV₁ was maintained with long-term administration, indicating that tachyphylaxis to long-term treatment with montelukast does not appear to occur. Tolerance, or loss of bronchoprotection from EIB, has been seen with LABAs. This loss of bronchoprotection appears to be a mechanism-based effect common to the inhaled β-agonists, and it has been suggested that this tolerance is due to an induced subsensitivity of the receptor caused by long-term β-agonist therapy. Importantly, the loss of bronchoprotection does not appear to be prevented by concomitant inhaled corticosteroids because tachyphylaxis to LABAs has been shown to occur in the presence of inhaled corticosteroids and even with use of high-dose SABA therapy.

In contrast, montelukast has been shown to provide and maintain meaningful protection from EIB. In a study of adults with concomitant asthma and EIB, montelukast had a significant effect on EIB that was sustained for 12 weeks. In 2 replicate studies conducted in adults to compare the bronchoprotective effects of montelukast vs salmeterol, montelukast demonstrated prevention of EIB that was similar to that of salmeterol within the first 3 days of initiating treatment but was significantly greater than salmeterol at week 4 and week 8 of treatment, which may be explained by tolerance to the effect of salmeterol with time.

Importantly, our study also demonstrated that the response to SABA rescue bronchodilatation for EIB was significantly better after montelukast treatment than after salmeterol treatment. Loss of effectiveness of SABAs as acute bronchodilator rescue therapy may be a safety concern in patients being treated in the long term with inhaled β-agonists. Specific evidence shows that albuterol provides limited bronchodilatation in patients receiving salmeterol. In a study specifically designed to compare the effects of adding montelukast or salmeterol to inhaled corticosteroids on the response to rescue SABA use after exercise challenge in adults, both the level and rapidity of the response to SABA rescue bronchodilatation was reduced in patients taking salmeterol but maintained in patients taking montelukast.

Evidence suggests that long-term administration of LABAs such as salmeterol may also diminish the magnitude of bronchoprotective effects against a variety of direct and other indirect bronchoconstrictor stimuli in adults. In addition, long-term use of salmeterol resulted in similar loss of protection against methacholine challenge in children and against exercise challenge in adolescents receiving corticosteroids. In some studies of long-term administration of LABAs, however, the prechallenge bronchodilatory responses were maintained, despite the decreased bronchoprotection after methacholine or exercise challenge.

In summary, montelukast significantly attenuated EIB compared with salmeterol after 4 weeks of treatment in patients 6 to 14 years old with persistent asthma receiving fluticasone. Response to SABA rescue after exercise challenge was significantly better with montelukast than with salmeterol. Addition of montelukast to a regimen of inhaled corticosteroids may afford more consistent protection against EIB than LABAs.

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REFERENCES


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