

## Letter to the Editor

**The effect of montelukast, budesonide alone, and in combination on exercise-induced bronchoconstriction**

To the Editor:

Current guidelines recommend regular inhaled corticosteroids (ICS) or alternatively cysteinyl leukotriene (CysLT) modifiers for the treatment of asthma.<sup>1</sup> The CysLT pathway has been shown to be important in the pathophysiology of exercise-induced bronchoconstriction (EIB).<sup>2</sup> However, the protection against EIB by CysLT modifiers alone is reported to be between 40% and 50%<sup>3-5</sup> with considerable between-subject variability. The rate of nonresponders across studies varies between 18% and 40%,<sup>6,7</sup> highlighting the heterogeneity in the mechanisms underlying EIB. Alternatively, ICS are potent anti-inflammatory agents that are highly effective in asthma, including alleviating EIB<sup>8</sup> but without any notable effect on the CysLT pathway.<sup>9</sup> These 2 agents have been directly compared only in 2 published trials using low- or high-dose ICS and showing conflicting results.<sup>4,5</sup> There are no data on medium-dose ICS and their combination with CysLT modifiers in EIB. Such information will extend our knowledge on the dose-response effect of ICS and its role in managing EIB.

In a 2-centers, randomized, double-blind, placebo-controlled, 4-arm cross-over study, the effect of montelukast 5 mg (<15 years old) or 10 mg daily for 2 weeks and budesonide 200 µg twice daily, alone or in combination, on EIB was examined. Subjects with asthma and EIB, not on maintenance therapy, and demonstrating a maximal fall in FEV<sub>1</sub> (maxFEV%) of 15% or more from baseline following 2 standardized exercise challenges during screening were enrolled (Table I). Details of the study methodology are provided in the Methods section and Fig E1 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org). There was a pre- and posttreatment visit for each period that was separated by a 4-week washout. Approval was obtained from each site's research ethics board and from all participants.

The severity of EIB was expressed as maxFEV% (pre-exercise FEV<sub>1</sub> minus lowest postexercise FEV<sub>1</sub>/pre-exercise FEV<sub>1</sub>) × 100 and area under the curve over 30 minutes postexercise (AUC-FEV<sub>0-30</sub>) by using the trapezoid rule. The changes between pre- and posttreatment visits were compared across treatments by using mixed-model analysis adjusted for period, centers, and pretreatment baseline. All *P* values (2 sided) were adjusted for multiple comparisons (Tukey method), and a value of .05 or less was considered significant. All analyses were performed by using SAS version 9.2 (SAS Institute, Cary, NC).

Data from 16 of the 25 randomized subjects (see Fig E2 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)) who completed all visits were analyzed. The subjects were predominantly atopic, with moderate to severe airway hyperresponsiveness to methacholine and exercise (Table I). There were no carryover effects or difference in the pretreatment spirometry or EIB measures across treatment periods. Placebo treatment did not affect the exercise airway responses. All active treatments caused a significant reduction in maxFEV% compared with placebo, but no significant difference was detected between the active treatments (Table I; Fig 1). In contrast, the improvement in

AUC-FEV<sub>0-30</sub> with combination therapy was significantly better than with its monocomponents. The nonresponder rate (ie, number of subjects with a maxFEV% attenuation ≤25%) following budesonide, montelukast, and combination therapy was 7, 6, and 2 and for AUC-FEV<sub>0-30</sub> 12, 13, and 9, respectively (combination vs montelukast, *P* = .03; combination vs budesonide,  $\chi^2$  test, *P* = .002).

Only 2 previous studies have directly compared the effect of montelukast and ICS on EIB.<sup>4,5</sup> The first study<sup>5</sup> showed that high-dose (800 µg/day) budesonide for 2 weeks was superior than 3 days of montelukast in asthmatic subjects aged 8 to 36 years with EIB. In the second study,<sup>4</sup> 4 weeks of montelukast (5 or 10 mg/day) alone or in combination with low-dose budesonide (200 µg/day) provided greater protection than budesonide alone in asthmatic children (6-18 years). Furthermore, no difference was found between combination therapy and montelukast monotherapy, suggesting that the addition of low-dose budesonide provided no added benefit. The current study found that medium-dose budesonide (400 µg/day) had an effect on maxFEV% that was comparable to that of montelukast, but the combination was better in improving the AUC-FEV<sub>0-30</sub> and providing faster recovery time. Moreover, the number of subjects with no improvement in EIB (attenuation ≤25%) was significantly lower with combination therapy. This effect is likely to be clinically relevant as it translates to a lower rate of treatment failures with combination therapy. These findings suggest a dose-response effect of ICS on EIB, and since high-dose ICS is generally not preferred, combination therapy with montelukast and medium-dose ICS may be considered for moderate to severe EIB.

Failure to respond to montelukast or ICS alone is commonly observed in clinical trials<sup>5-7</sup> and highlights the complex and diverse mechanisms that underlie EIB. Combining agents that target different pathophysiological pathways may improve the rate of clinical response. However, this approach needs to be carefully weighed against the potential impact on cost and the rate of side effects and compliance. As our sample size was small, we did not further explore for factors that might predict response to one treatment over the other. However, other studies have demonstrated increase in montelukast responsiveness in subjects with lower methacholine airway hyperresponsiveness and IgE levels<sup>7</sup> and genetic polymorphisms of the thromboxane A<sub>2</sub> receptor<sup>10</sup> and IL-13.<sup>11</sup> Alternatively, predictors for ICS response have not been extensively studied. In previous studies, we found that EIB with airway eosinophilia showed a greater response to ICS than did EIB without eosinophilia.<sup>12</sup> Furthermore, the effect of ICS was dose- and time-dependent in subjects with sputum eosinophilia. All doses of ICS induced a significant reduction in maxFEV% at 1 week and reached maximal effect by 2 weeks on low- to medium-ICS doses.<sup>13</sup> However, in subjects with airway eosinophilia, further improvement in EIB was observed beyond 2 weeks with high-dose ICS, indicating that these patients may benefit from high-dose and longer duration of ICS treatment. Therefore, sputum eosinophil levels may serve as a useful marker for ICS responsiveness in patients with EIB.

Compared with previous studies,<sup>4,5</sup> the effect of the active therapies that we report is smaller, which may relate to certain

**TABLE I.** Baseline subject characteristics and individual exercise responses to treatments

| ID                                                      | Age/sex | Baseline characteristics |     |                      |                  |                       | maxFEV <sub>1</sub> (%) |                     |
|---------------------------------------------------------|---------|--------------------------|-----|----------------------|------------------|-----------------------|-------------------------|---------------------|
|                                                         |         | Triggers                 | Sym | MethPC <sub>20</sub> | FEV <sub>1</sub> | maxFEV <sub>1</sub> % | P                       | B                   |
| A1                                                      | 16F     | 0                        | 0   | 1.47                 | 79               | 19.7                  | 13.7                    | 7.0                 |
| A2                                                      | 21F     | AP                       | 1-3 | 0.58                 | 100              | 19.3                  | 37.3                    | 16.6                |
| A3                                                      | 21M     | APH                      | 0   | 0.53                 | 100              | 15.0                  | 17.8                    | 15.6                |
| A4                                                      | 16M     | APH                      | 0   | 8.51                 | 105              | 42.3                  | 34.0                    | 4.7                 |
| B1                                                      | 10M     | APH                      | 1-3 | 1.00                 | 81               | 28.0                  | 5.1                     | 31.6                |
| B2                                                      | 25M     | APH                      | 0-1 | 1.00                 | 101              | 47.1                  | 16.3                    | 28.1                |
| B3                                                      | 28F     | APH                      | 0-1 | 8.00                 | 108              | 18.6                  | 23.8                    | 2.5                 |
| B4                                                      | 16M     | APH                      | >3  | 2.00                 | 102              | 28.8                  | 20.7                    | 9.5                 |
| B5                                                      | 33F     | APH                      | >3  | 2.00                 | 74               | 17.9                  | 15.0                    | 8.0                 |
| B6                                                      | 11M     | APH                      | 0-1 | 0.25                 | 83               | 22.0                  | 38.3                    | 10.4                |
| B7                                                      | 14M     | 0                        | 0-1 |                      | 74               | 30.9                  | 25.0                    | 24.1                |
| B8                                                      | 10F     | APH                      | 1-3 | 0.50                 | 101              | 60.3                  | 38.4                    | 18.9                |
| B9                                                      | 10F     | APH                      | 1-3 | 0.06                 | 89               | 35.2                  | 36.6                    | 37.6                |
| B10                                                     | 16M     | APH                      | 1-3 | 0.12                 | 75               | 64.1                  | 66.7                    | 75.0                |
| B11                                                     | 11F     | AP                       | 0   | 1.00                 | 95               | 39.1                  | 38.4                    | 8.0                 |
| B12                                                     | 12F     | APH                      | 1-3 | 2.00                 | 76               | 16.2                  | 23.6                    | 36.0                |
| Pretreatment                                            |         |                          |     | 0.9*<br>(0.4, 1.9)   | 90 ± 3           | 31.5 ± 4              | 27.5 ± 3                | 26.6 ± 4            |
| Posttreatment                                           |         |                          |     |                      |                  |                       | 28.2 ± 4                | 20.8 ± 5            |
| Difference in pre-post treatment change to placebo†     |         |                          |     |                      |                  |                       |                         | 7.8 ± 2<br>(1, 15)‡ |
| Difference in pre-post treatment change to budesonide†  |         |                          |     |                      |                  |                       |                         |                     |
| Difference in pre-post treatment change to montelukast† |         |                          |     |                      |                  |                       |                         |                     |

Data are presented as means ± SEs (95% CI), unless indicated otherwise.

Prefixes A and B in subject ID denote the study center.

Triggers represent known precipitants reported by subjects to cause asthma symptoms other than exercise and confirmed by a modified skin prick test with a wheal reaction of more than 2 × 2. A, Animal dander (dog, cat, horse, feather), P, pollens (tree, grass, ragweed), H, house dust mites.

Attenuation and improvement were calculated as (pretreatment minus posttreatment)/pretreatment × 100. Negative sign indicates a worsening.

AUC-FEV<sub>0-30</sub>, Area under the curve for FEV<sub>1</sub> fall postexercise up to 30 minutes; B, budesonide; B + M, combination therapy; F, female; M, male; M, montelukast; maxFEV<sub>1</sub>%, maximal FEV<sub>1</sub> fall from pre-exercise level (pre-exercise FEV<sub>1</sub> minus lowest postexercise FEV<sub>1</sub>)/pre-exercise FEV<sub>1</sub> × 100; Meth PC<sub>20</sub> (mg/mL), methacholine concentration causing a 20% fall in FEV<sub>1</sub> from prechallenge level; P, placebo; Sym, average number of days and nights with symptoms per week including exercise-induced episodes.

\*Geometric mean (95% CI).

†Estimates represent pre-post treatment difference between treatments by least squares means in mixed model approach adjusting for pretreatment baseline, period, and centers.

‡P < .05.

§P < .005.

aspects of the subjects' characteristics. Our subjects demonstrated severe baseline EIB (maxFEV<sub>1</sub> 31.5% ± 3.9%) and were atopic, which may result in frequent fluctuations in asthma control throughout the long duration of the study (24 weeks). There was also heterogeneity in the asthmatic phenotype studied, with a range of age, duration of asthma, and severity of airway hyperresponsiveness that may influence the degree of therapy response.<sup>12,14</sup> All these factors increase the variability in the treatment response between and within subjects and reduce the effect size of the treatments. On the other hand, the inclusion of a wide range of subjects and conditions increases the generalizability of our findings.

Our study has a few limitations. The sample size was small, and larger efficacy and cost-effectiveness studies are needed before these findings can be recommended. We did not examine other recommended therapies such as long-acting beta agonist since our interest was in therapies that target the underlying mechanisms. Furthermore, even though the effect of long-acting beta agonist and long-acting beta agonist-ICS combination is highly effective in protecting against EIB<sup>15,16</sup> in the short term, their long-term bronchoprotective benefit remains uncertain.<sup>17,18</sup>

In conclusion, montelukast or medium-dose ICS, alone or in combination, in severe EIB provided comparable and modest attenuation in maxFEV<sub>1</sub>. However, combination therapy offered an added benefit of a shorter duration and time to recovery from EIB, and a higher rate of response that suggest that single-agent therapy may not be sufficient to combat the complex and heterogeneous pathophysiological pathways that underlie severe EIB in asthma.

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TABLE I. (Continued)

| maxFEV% (%) |          | maxFEV% attenuation (%) |        |        | AUC-FEV <sub>0-30</sub> (L × min) |          |             |           | AUC-FEV <sub>0-30</sub> improvement (%) |        |        |
|-------------|----------|-------------------------|--------|--------|-----------------------------------|----------|-------------|-----------|-----------------------------------------|--------|--------|
| M           | B + M    | B                       | M      | B + M  | P                                 | B        | M           | B + M     | B                                       | M      | B + M  |
| 13.1        | 5.6      | 70                      | 40     | 68     | 92.6                              | 90.6     | 94.9        | 92.9      | 9                                       | 2      | 1      |
| 24.5        | 6.5      | 32                      | 39     | 77     | 78.0                              | 93.9     | 82.9        | 102.5     | 10                                      | 33     | 61     |
| 13.0        | 11.7     | 50                      | 54     | 72     | 91.3                              | 92.9     | 103.6       | 95.8      | 27                                      | 47     | 54     |
| 11.5        | 15.0     | 77                      | 66     | 42     | 85.0                              | 111.0    | 99.8        | 104.7     | 17                                      | 15     | 17     |
| 1.1         | 9.6      | −39                     | 79     | 49     | 52.6                              | 44.7     | 53.8        | 52.6      | −1                                      | 1      | 6      |
| 9.4         | 17.1     | −134                    | 66     | 51     | 135.3                             | 145.0    | 165.5       | 153.4     | −9                                      | 15     | 14     |
| 12.9        | 6.5      | 84                      | 19     | 56     | 95.2                              | 108.2    | 106.2       | 112.1     | 9                                       | 4      | 8      |
| 6.4         | 11.5     | 17                      | 61     | 43     | 92.9                              | 102.2    | 105.8       | 102.8     | −3                                      | 9      | 16     |
| 14.9        | 16.9     | 37                      | −35    | −8     | 53.0                              | 54.6     | 55.0        | 59.0      | −3                                      | 2      | −1     |
| 20.3        | 9.6      | 57                      | 45     | 41     | 51.9                              | 51.6     | 42.2        | 57.4      | 6                                       | −10    | 32     |
| 14.3        | 37.3     | −36                     | 65     | 11     | 87.2                              | 92.9     | 84.7        | 70.6      | −1                                      | 0.0    | 2      |
| 46.9        | 35.8     | 67                      | 26     | 37     | 49.8                              | 57.3     | 45.0        | 61.8      | 58                                      | 41     | 59     |
| 35.4        | 18.1     | 4                       | 7      | 40     | 59.5                              | 51.3     | 58.8        | 71.2      | 28                                      | 18     | 37     |
| 63.0        | 44.2     | −15                     | 10     | 35     | 41.5                              | 33.3     | 40.6        | 72.9      | −25                                     | −1.0   | 104    |
| 19.3        | 14.9     | 64                      | 19     | 39     | 52.4                              | 63.1     | 63.6        | 72.7      | 27                                      | 12     | 26     |
| 22.7        | 10.3     | −47                     | −59    | 64     | 43.3                              | 47.6     | 40.6        | 47.2      | 15                                      | −5     | 10     |
| 30.5 ± 4    | 30.3 ± 4 |                         |        |        | 72.0 ± 7                          | 72.2 ± 8 | 69.8 ± 7    | 67.6 ± 7  |                                         |        |        |
| 20.6 ± 4    | 16.9 ± 3 | 18 ± 2                  | 31 ± 9 | 45 ± 5 | 72.6 ± 6                          | 77.5 ± 8 | 77.7 ± 8    | 83.1 ± 7  | 10 ± 5                                  | 11 ± 4 | 28 ± 7 |
| 11 ± 2      | 12 ± 3   |                         |        |        |                                   | 0.15 ± 1 | 7.3 ± 2     | 10.2 ± 2  |                                         |        |        |
| (4, 18)§    | (3, 12)§ |                         |        |        |                                   | (−3, 4)  | (2, 13)‡    | (4, 16)§  |                                         |        |        |
| −3.2 ± 2    | 3.7 ± 2  |                         |        |        |                                   |          | 7.2 ± 2     | 10.1 ± 2  |                                         |        |        |
| (−10, 4)    | (−3, 10) |                         |        |        |                                   |          | (0.06, 14)‡ | (4, 17)§  |                                         |        |        |
|             | 0.5 ± 2  |                         |        |        |                                   |          |             | 2.9 ± 1   |                                         |        |        |
|             | (−7, 8)  |                         |        |        |                                   |          |             | (0.1, 6)‡ |                                         |        |        |

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## REFERENCES

- Weiler JM, Bonini S, Coifman R, et al. American Academy of Allergy, Asthma & Immunology Work Group report: exercise-induced asthma. *J Allergy Clin Immunol* 2007;119:1349-58.
- Hallstrand TS, Henderson WR Jr. Role of leukotrienes in exercise-induced bronchoconstriction. *Curr Allergy Asthma Rep* 2009;9:18-25.
- Kemp JP, Dockhorn RJ, Shapiro GG, Nguyen HH, Reiss TF, Seidenberg BC, et al. Montelukast once daily inhibits exercise-induced bronchoconstriction in 6- to 14-year-old children with asthma. *J Pediatr* 1998;133:424-8.
- Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. *J Allergy Clin Immunol* 2008;121:383-9.
- Vidal C, Fernandez-Ovide E, Pineiro J, Nunez R, Gonzalez-Quintela A. Comparison of montelukast versus budesonide in the treatment of exercise-induced bronchoconstriction. *Ann Allergy Asthma Immunol* 2001;86:655-8.
- Melo RE, Sole D, Naspitz CK. Exercise-induced bronchoconstriction in children: montelukast attenuates the immediate-phase and late-phase responses. *J Allergy Clin Immunol* 2003;111:301-7.
- Lee SY, Kim HB, Kim JH, Kim BS, Kang MJ, Jang SO, et al. Responsiveness to montelukast is associated with bronchial hyperresponsiveness and total immunoglobulin E but not polymorphisms in the leukotriene C4 synthase and cysteinyl leukotriene receptor 1 genes in Korean children with exercise-induced asthma (EIA). *Clin Exp Allergy* 2007;37:1487-93.
- Koh MS, Tee A, Lasserson TJ, Irving LB. Inhaled corticosteroids compared to placebo for prevention of exercise induced bronchoconstriction. *Cochrane Database Syst Rev* 2007;3:CD002739.
- Peters-Golden M, Sampson AP. Cysteinyl leukotriene interactions with other mediators and with glucocorticosteroids during airway inflammation. *J Allergy Clin Immunol* 2003;111:S37-42, discussion S3-8.
- Kim JH, Lee SY, Kim HB, Jin HS, Yu JH, Kim BJ, et al. *TBXA2R* gene polymorphism and responsiveness to leukotriene receptor antagonist in children with asthma. *Clin Exp Allergy* 2008;38:51-9.
- Kang MJ, Lee SY, Kim HB, Yu J, Kim BJ, Choi WA, et al. Association of IL-13 polymorphisms with leukotriene receptor antagonist drug responsiveness in Korean children with exercise-induced bronchoconstriction. *Pharmacogenet Genomics* 2008;18:551-8.
- Duong M, Subbarao P, Adelroth E, Obminski G, Strinich T, Inman M, et al. Sputum eosinophils and the response of exercise-induced bronchoconstriction to corticosteroid in asthma. *Chest* 2008;133:404-11.
- Subbarao P, Duong M, Adelroth E, Otis J, Obminski G, Inman M, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. *J Allergy Clin Immunol* 2006;117:1008-13.

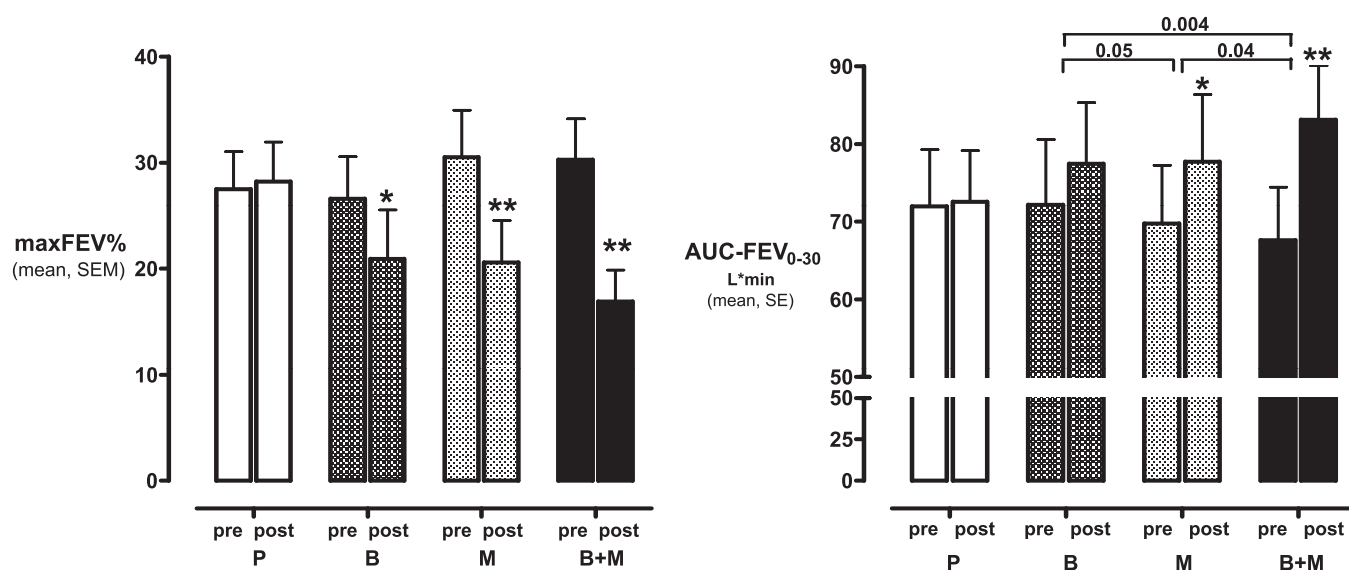


**FIG 1.** Pre- and posttreatment values for maximal fall in FEV<sub>1</sub> (maxFEV%) and area under the curve for FEV<sub>1</sub> over 30 minutes (AUC-FEV<sub>0-30</sub>) for each treatment. B, Budesonide; B + M, combination therapy; M, montelukast; P, placebo. Changes following treatment compared with placebo at \* $P < .05$  and \*\* $P \leq .005$ .

14. Szefer SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol* 2005;115:233-42.
15. Pearlman D, Qaqundah P, Matz J, Yancey SW, Stempel DA, Ortega HG. Fluticasone propionate/salmeterol and exercise-induced asthma in children with persistent asthma. *Pediatr Pulmonol* 2009;44:429-35.
16. Weiler JM, Natahn RA, Rupp NT, Kalberg CJ, Emmett A, Dorinsky PM. Effect of fluticasone/salmeterol administration via a single device on exercise-induced bronchospasm in patients with persistent asthma. *Ann Allergy Asthma Immunol* 2005;94:65-72.
17. Simons FE, Gerstner TV, Cheang MS. Tolerance to the bronchoprotective effect of salmeterol in adolescents with exercise-induced asthma using concurrent inhaled glucocorticoid treatment. *Pediatrics* 1997;99:655-9.
18. Villaran C, O'Neill SJ, Helbling A, van Noord JA, Lee TH, Chuchalin AG, et al. Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. Montelukast/Salmeterol Exercise Study Group. *J Allergy Clin Immunol* 1999;104:547-53.

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## METHODS

This was a randomized, double-blind, placebo-controlled 4-period cross-over-study conducted in 2 centers from March 2007 to June 2009. The inclusion criteria included a history of physician-diagnosed asthma for more than 6 months, age between 8 and 35 years, baseline FEV<sub>1</sub> of 70% or more of predicted, and a history of exercise-induced symptoms with a maximal fall in FEV<sub>1</sub> (maxFEV%) of 15% or more from the prechallenge level following a standardized exercise challenge on 2 screening visits separated by 1 week. Exclusion criteria included recent worsening of asthma in the preceding 6 weeks, regular use of asthma medications other than as-needed salbutamol, significant comorbidity, and a cigarette smoking history of 10 or more pack-years. Subjects attended 10 visits over 21 to 24 weeks that included 2 screening visits and 8 treatment visits that were scheduled before and after each 2 weeks of treatments. There was a washout interval of 4 to 6 weeks in between periods to allow the return of exercise responses to pretreatment levels (Fig E1). At each visit, subjects underwent a standardized exercise challenge and pre- and postexercise spirometry. In addition, a methacholine inhalation challenge and a modified skin prick test were performed during the screening visits. The 4 treatment arms were montelukast sodium 5 mg (for <15 years old) or 10 mg daily, budesonide 200 µg twice daily, montelukast and budesonide combination, and matching placebos. The last dose of medications was taken at least 8 hours prior to the posttreatment visits.

Spirometry was performed according to ATS standards<sup>E1</sup> and reference values taken from Hankinson et al.<sup>E2</sup> Exercise challenge<sup>E3</sup> was performed on a treadmill for 8 minutes with continuous heart rate monitoring and breathing dry air (temperature 21°C, relative humidity <10%). The speed and incline of the treadmill was adjusted to achieve 90% of the predicted maximum heart rate (210 minus age) for the last 4 minutes of the test. After the test, subjects continued to walk for a further 2 minutes while breathing dry air. FEV<sub>1</sub> was measured pre-exercise and 2, 4, 6, 8, 10, 15, 20, and 30 minutes postexercise. The severity of EIB was expressed as maxFEV% (pre-exercise FEV<sub>1</sub> minus lowest FEV<sub>1</sub> postexercise/pre-exercise FEV<sub>1</sub>) × 100 and area under the curve

over 30 minutes postexercise (AUC-FEV<sub>0-30</sub>), calculated by using the trapezoid rule. Methacholine test was performed by using the tidal breathing method.<sup>E4</sup> A modified skin prick test with 14 common aeroallergens<sup>E5</sup> was used to establish a positive reaction of 2 × 2 mm wheal at 15 minutes.

Data are presented as means ± SEMs (95% CI). Only subjects who completed all treatment visits were included in the per-protocol analysis. The changes between pre- and posttreatment visits across treatments were compared by using a mixed-model approach<sup>E6</sup> adjusted for treatment period, center, and pretreatment baseline. All *P* values (2 sided) were adjusted for multiple comparisons (Tukey method), and value of .05 or less was considered significant. All analyses were performed by using SAS version 9.2 (SAS Institute, Cary, NC).

A sample size of 14 subjects was calculated to detect a 25% (95% power and alpha level <0.05) difference in maxFEV% between any of the 2 treatments with an estimated within-subject SD of 15% (previously shown in our laboratory) on exercise challenge.

## REFERENCES

- E1. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
- E2. Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med* 1999;159:179-87.
- E3. Subbarao P, Duong M, Adelroth E, Otis J, Obminski G, Inman M, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. *J Allergy Clin Immunol* 2006;117:1008-13.
- E4. Juniper EFCD, Hargreave FE. Histamine and methacholine inhalation tests; a laboratory tidal breathing protocol. ASTRA DRACO AB. Lund, Sweden; 1994.
- E5. Pepys J. Clinical aspects of immunology. 3rd ed. Oxford: Blackwell Scientific Publications; 1975.
- E6. Jones B, Kenward MG. Design and analysis of cross-over trials (Chapman & Hall/CRC Monographs on Statistics & Applied Probability). Second ed: Florida: Chapman & Hall/CRC; 2003.

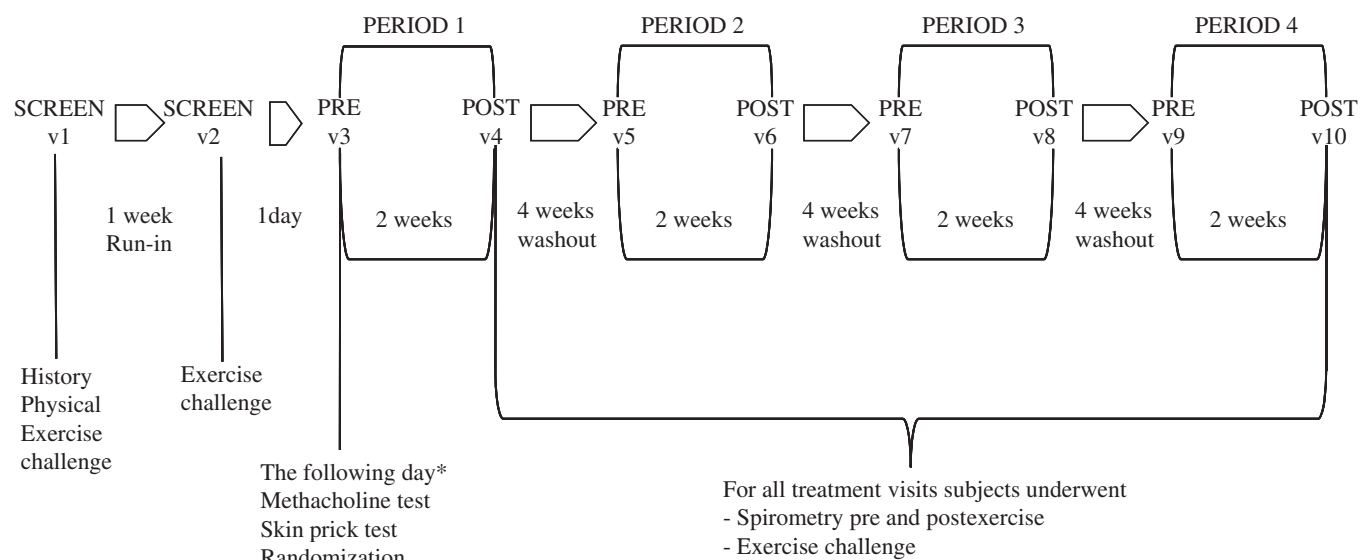
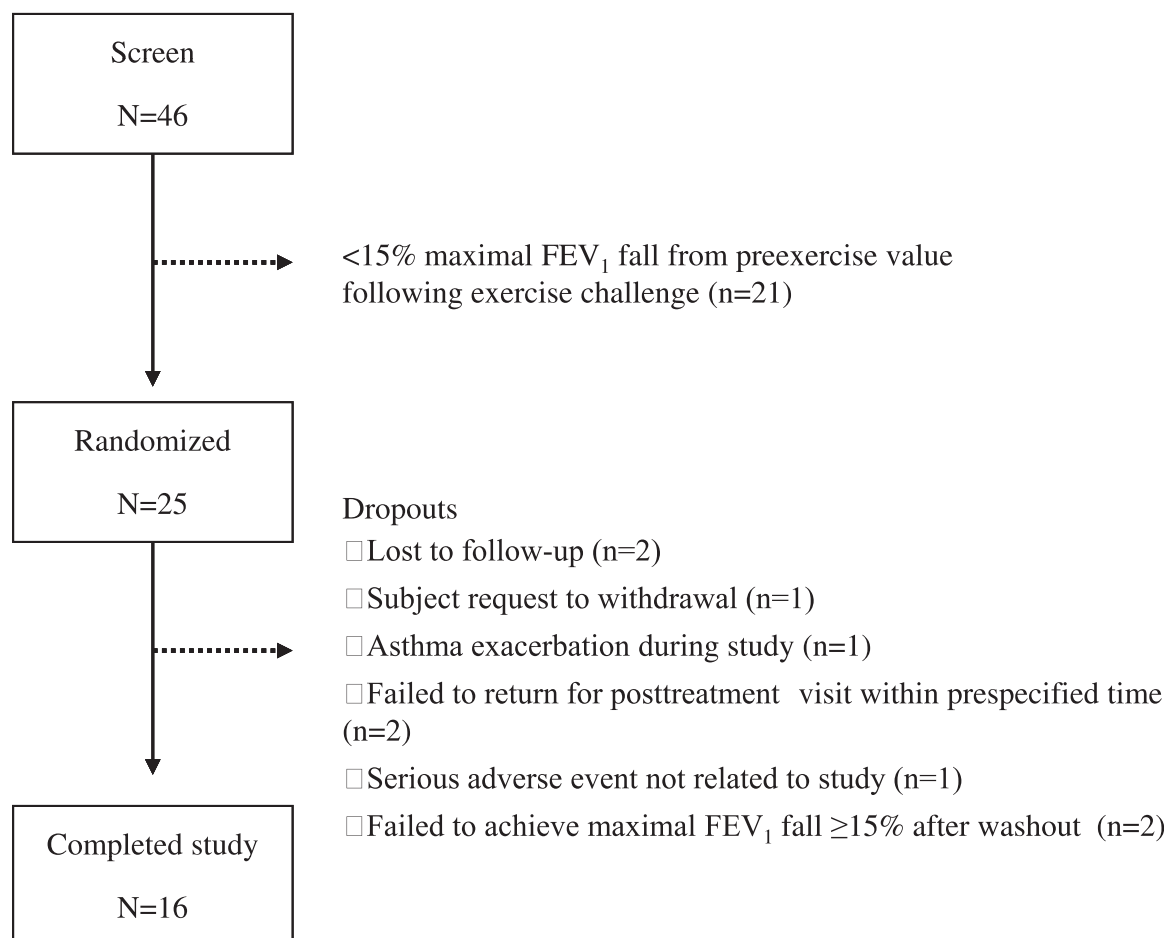


**FIG E1.** Flow diagram of study design. At the first screening visit, an exercise challenge was performed followed in 1 week by a second screening visit with an exercise challenge. Qualified subjects return the following day\* for a methacholine and skin prick test and are randomized to the first treatment. Each treatment period was for 2 weeks with a pretreatment (*PRE*) and posttreatment (*POST*) visit and a washout of 4 to 6 weeks between treatment periods. Treatments were matching placebos, montelukast 5/10 mg, budesonide 400  $\mu$ g, or montelukast + budesonide.

**FIG E2.** Flowchart of enrolled subjects.