

Effects of montelukast and beclomethasone on airway function and asthma control

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Background: Maintaining asthma control is a major objective of therapy. Traditionally, the effectiveness of asthma therapy has been judged primarily by its effect on airway function rather than on multiaspect asthma control.

Objective: An inhaled corticosteroid and a leukotriene receptor antagonist were compared to determine whether they provided equivalent effects, as judged by days of asthma control. **Methods:** In a randomized, multicenter, double-blind, placebo-controlled, parallel-group study, asthmatic patients ($n = 782$) with FEV₁ percent predicted values of between 50% and 85% and a weekly average β -agonist use of more than 2 puffs per day were randomized to receive montelukast (10 mg daily), beclomethasone (200 μ g twice daily), or placebo treatment for 6 weeks in a double-dummy fashion. We examined the distribution of the primary end point: percentage of days of asthma control. Secondary end points included FEV₁, albuterol use, occurrence of an asthma attack, asthma flare-up, rescue corticosteroid use, sustained asthma control, and adverse experiences. **Results:** The percentage of days of asthma control was almost identical between the montelukast and beclomethasone groups (98% overlap in the distribution). Montelukast was at least equal to beclomethasone, and both were greater than placebo on the basis of frequency of asthma attacks, asthma flare-ups, and rescue corticosteroid use. Beclomethasone had a greater effect than montelukast and both treatments were better than placebo at improving FEV₁.

Conclusions: Montelukast was as effective as beclomethasone, as judged by indices of clinical control other than FEV₁. When evaluating the outcome of montelukast therapy, FEV₁ might

underestimate clinical effectiveness. (*J Allergy Clin Immunol* 2002;110:847-54.)

Key words: Montelukast, beclomethasone, asthma

Asthma is an inflammatory disease leading to episodic worsening of airway function, mucus production, cough, and other symptoms.¹ According to the National Asthma Education and Prevention Program asthma treatment guidelines,¹ drugs capable of providing long-term control of asthma are indicated when symptoms become persistent. Inhaled corticosteroids (ICSs) are often recommended as initial controller therapy for the management of persistent asthma because of their anti-inflammatory effects and proven benefits. However, the inhaled form of drug delivery is associated with lower adherence to therapy compared with that seen with drug delivered by means of the oral route,^{2,3} and many patients experience difficulty in using inhaled therapy.⁴

Several large clinical trials in adults with chronic asthma have documented the beneficial effects of oral montelukast, a leukotriene receptor antagonist, in improving asthma outcomes (eg, decreased asthma exacerbations), asthma symptoms, and lung function.⁵⁻⁷ Additionally, studies in asthmatic adults and children have demonstrated that adherence to therapy is substantially greater with oral montelukast than with inhaled asthma therapy.⁸⁻¹⁰

Although the objective of chronic therapy for asthma is to minimize symptoms and to avoid asthma exacerbations, typical assessment is based on conventional measures of airway function. Measurement of asthma control should include the need for rescue medications or unscheduled asthma-related health care.¹¹ When defined in this way, a measure of days of asthma control correlates with patient symptoms.¹² Consecutive days with asthma flare-ups should be avoided.¹³

The primary objective of the present study was to compare the effects of the 2 therapies (montelukast and beclomethasone), as judged by days of asthma control. A placebo group was included to demonstrate that both treatment arms produced salutary effects. Secondary variables included FEV₁, β -agonist use, asthma attacks and flare-ups, days of sustained asthma control, and rescue corticosteroid use.

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Abbreviation used

ICS: Inhaled corticosteroid

METHODS**Study design**

This was a multicenter, randomized, parallel-group study consisting of a 1-week prestudy screening period, a 2-week single-blind placebo baseline period, and a 6-week double-blind treatment period. A 6-week treatment period was chosen because it has been shown to be a sufficient period of time to achieve most of the effects of these 2 therapies.⁷ Clinic visits were scheduled at the end of the 1-week prestudy screening period, at the end of the 2-week single-blind period, and every 3 weeks during double-blind therapy.

The study was conducted at 64 study centers in the United States between August 1997 and March 1998. The 782 eligible patients were randomly assigned, according to a blinded allocation schedule produced by the study sponsor, to receive either montelukast sodium (10-mg tablet once daily in the evening), beclomethasone dipropionate (200 µg [4 puffs] twice daily administered by means of inhalation), or placebo in a 3:3:1 patient ratio, respectively. Each patient received one tablet daily (active or matching placebo) and one inhaler dose twice daily (active or matching placebo) for both the single-blind and double-blind treatment periods. The use of a spacer device was permitted and was not provided; data regarding spacer use were not collected. Each study center was provided with a block of allocation numbers that were assigned sequentially to consecutively randomized patients.

The protocol for this study was approved by the institutional review board of each site, and written informed consent was obtained from each patient. If the patient was younger than 18 years, written consent was obtained from the patient, as well as from the patient's parent or guardian.

Inclusion and exclusion criteria

Male and female patients at least 15 years of age with at least a 1-year history of clinical symptoms of asthma were enrolled in the study. Women of childbearing age were required to have a negative serum β -human chorionic gonadotropin test at the prestudy visit. Patients' asthma treatment could include only short-acting β -agonist (albuterol) at the time of randomization. Patients were eligible for randomization if they had an FEV₁ of between 50% and 85% of the predicted value at rest and at least a 15% increase in FEV₁ after albuterol administration (demonstrated twice during the single-blind run-in period). In addition, all patients were required to have average albuterol use of greater than 2 puffs per day (which might include those for exercise prophylaxis) during the baseline run-in period. Eligible patients were nonsmokers for at least 1 year before enrollment, with a smoking history of no more than 7 pack-years.

Patients with upper respiratory tract infections within the past 3 weeks, emergency care for asthma within 1 month, or hospitalization for asthma within 3 months were excluded. Systemic corticosteroids were not allowed for 1 month before the first study visit; ICSs were not allowed for 2 weeks before the first study visit. Patients were required to stop other antiasthma therapy 1 week before the first study visit. Inhaled albuterol for symptomatic relief of asthma and short-acting antihistamines were permitted. According to a standard action plan, up to 2 uses of rescue oral corticosteroid for the treatment of worsening asthma were allowed during the double-blind period. Patients who needed additional oral corticosteroid treatment discontinued study therapy.

Evaluations

Subjects completed daily diary cards throughout the single-blind run-in period and the 6-week double-blind treatment period. The

daily diary cards collected information on asthma attacks (patient indicated yes or no), nighttime awakening,¹⁴ and albuterol use (number of puffs per day).

A day of asthma control was defined as a day with no more than 2 puffs of albuterol (including those for exercise prophylaxis), no nighttime awakenings, and no asthma attacks. Nocturnal awakening was evaluated on the basis of the patient's response to a single question with a 4-point scale (no awakenings = 0, awake all night = 4). An asthma attack was defined, as in previous studies,^{5,7} as worsening asthma resulting in an unscheduled visit to the doctor's office or emergency department, hospitalization, or treatment with oral corticosteroids. An asthma flare-up was defined as a period of at least 3 consecutive days that did not meet the definition of a day of asthma control. An occurrence of sustained asthma control was defined as a period of at least 3 consecutive days of asthma control.

Spirometry was performed at every visit during single-blind and double-blind therapy according to American Thoracic Society acceptability and reproducibility criteria by using a standard spirometer (Puritan-Bennett PB 100/PB110, Wilmington, Mass).¹⁵ Patients were required to withhold the use of inhaled albuterol for 6 hours before the visit. At each visit during the double-blind period, all spontaneously reported adverse experiences were recorded, and daily peak flow measurements were reviewed. Adherence with treatment was measured at the last study visit on the basis of study medication tablet count and patient recall of inhaler use.

Statistical methods

The prespecified primary end point was the percentage of days of asthma control during the 6 weeks of double-blind treatment. Secondary end points were average daily albuterol use, percentage of patients with or without an asthma attack, asthma flare-up, occurrence of sustained asthma control, rescue corticosteroid use, and change from baseline in FEV₁. The frequency of adverse experiences was also evaluated.

Analysis. The prespecified analysis for the primary end point was the overlap between treatment groups in the distributions of patient response. The comparison of the full range of efficacy responses in the 2 active treatment groups provides valuable information that extends beyond the comparison of group mean data; the overlap method was developed to provide a statistical treatment of this comparison. The overlap was analyzed for percentage of days of asthma control (primary end point) and change in FEV₁ (secondary end point) by using a modification of the nonparametric Mann-Whitney *U* test.^{16,17} The *U** statistic estimates the probability that a randomly chosen patient in the inhaled beclomethasone group will experience a greater treatment effect than a randomly chosen patient in the montelukast group and was expressed as a percentage overlap of response distributions, as previously described.¹⁸ The Mann-Whitney *U* test is equivalent to the frequently used nonparametric Wilcoxon rank sum test.¹⁹

Between-group comparisons of mean values were performed for days of asthma control, change from baseline in FEV₁, and average daily β -agonist use by using ANOVA. A logistic-regression model was used to analyze patients with or without asthma attacks, asthma flare-ups, episodes of sustained asthma control, and rescue corticosteroid use. The percentage of days of asthma control ([Sum of total days that were part of a sustained asthma control episode/Days in study] $\times$ 100) was analyzed in a similar manner as the primary end point. The Fisher exact test was used to compare overall between-group incidence of clinical and laboratory adverse experiences.

An all-patients-treated approach was used in the analyses of efficacy data, whereby all patients with a baseline and at least one post-randomization measurement were included in the group to which they were randomized, regardless of adherence to the protocol. For the analysis of change in FEV₁, missing values at the end of the

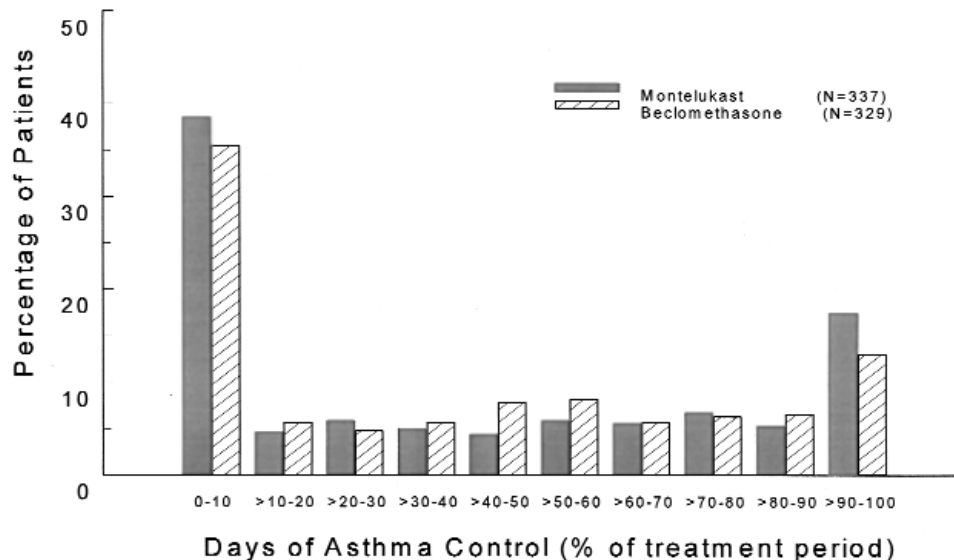


FIG 1. Frequency distributions of days of asthma control (expressed as percentage of days during the 6-week treatment period) for montelukast and beclomethasone. The overlap between montelukast and beclomethasone in the patient response distributions for days of asthma control was 97.7% (95% CI, 89.0-100.0).

study were imputed by carrying forward the most recent measured value during the double-blind treatment period. Descriptive statistics were computed by treatment group for patient demographics, clinical characteristics, and baseline profiles.

Power and sample size. Sample size planning was based on the percentage overlap in the distributions of the percentage of days of asthma control in a previous study, which was estimated to be 88.6% for the montelukast and beclomethasone groups.⁷ Assuming that the percentage overlap in the distribution of the percentage of days of asthma control was 88%, with 267 patients per active-treatment group, the study had 80% power to detect an overlap of 80% or greater. All statistical analyses were performed by using SAS⁹ version 6 software (SAS Institute, Inc, Cary, NC).

RESULTS

Patients

Seven hundred eighty-two patients from 64 study centers entered the double-blind period: 339 were allocated to montelukast, 332 to beclomethasone, and 111 to placebo. Baseline demographic characteristics were comparable among the 3 groups (Table I). Seven hundred fifty-two (96.2%) patients completed the 6-week double-blind study; 11 (3.2%) patients in the montelukast group, 14 (4.2%) patients in the beclomethasone group, and 5 (4.5%) patients in the placebo group prematurely discontinued therapy. There were no meaningful differences in the discontinuation rates among the 3 groups.

Days of asthma control

The percentage overlap of days of asthma control for montelukast and beclomethasone was 97.7% (95% CI, 89.0%-100%; Fig 1). The group mean values for the percentage of days of asthma control during the treatment period were 41.4% (95% CI, 37.4%-45.4%) for mon-

telukast, 41.1% (95% CI, 37.0%-45.3%) for beclomethasone, and 26.8% (95% CI, 20.0%-33.5%) for placebo. The difference between montelukast and beclomethasone with respect to the mean percentage of days of asthma control was not significant (0.24%, $P = .929$). For both montelukast and beclomethasone, the difference from placebo in the percentage of days of asthma control was significant (14.6% [$P < .001$] and 14.4% [$P < .001$], respectively; Table II). The effect of both therapies on asthma control days increased gradually with time (Fig 2).

Analyses of the individual components of an asthma control day were performed and were consistent with the primary end point of asthma control days (data not shown). β -Agonist use was responsible for the greatest percentage of noncontrol days (45.2% and 44.4% in the montelukast and beclomethasone groups, respectively).

Average daily β -agonist (albuterol) use

Compared with the placebo group, both the montelukast and beclomethasone groups reduced average daily β -agonist use ($P < .001$ for each comparison, Table II). The therapies did not differ from each other in this effect ($P = .621$).

Asthma attacks and asthma flare-up

Fig 3 displays a Kaplan-Meier plot of the time to first asthma attack for each treatment group during the 6-week treatment period. Compared with the placebo group, the montelukast group had significantly fewer patients who experienced an asthma attack ($P = .025$). The beclomethasone group, however, trended toward significance ($P = .089$). The therapies did not differ from each other in the percentage of patients who experienced an asthma attack ($P = .488$, Table II).

Asthma, rhinitis,
other respiratory
diseases

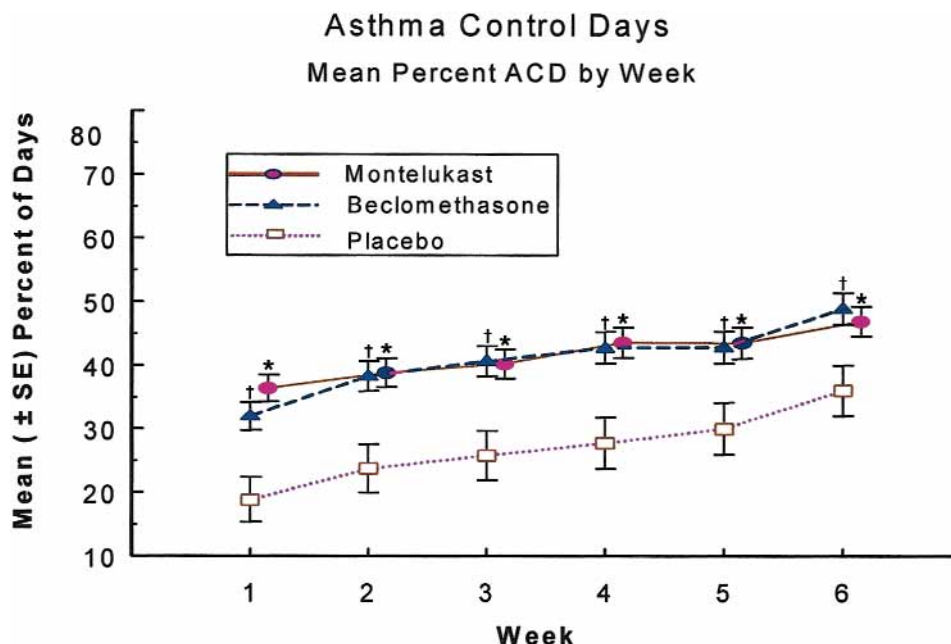


FIG 2. Mean percentage of asthma control days (expressed by week) for montelukast, beclomethasone, and placebo. * $P < .05$ versus placebo; † $P < .05$ versus placebo.

TABLE I. Baseline demographics and clinical characteristics

	Montelukast (n = 339)	Beclomethasone (n = 332)	Placebo (n = 111)
Age, y (mean [range])	33.5 (15-71)	33.9 (15-74)	33.3 (15-64)
Female (%)	52.2	53.0	51.4
White (%)	87.6	81.9	88.3
Black (%)	5.9	6.0	7.2
Hispanic (%)	4.1	6.9	3.6
Other racial origin (%)	2.4	5.1	0.9
Asthma duration, y (mean ± SD)	18.8 ± 11.9	18.3 ± 13.1	21.4 ± 13.5
FEV ₁ , L (mean ± SD)	2.5 ± 0.6	2.5 ± 0.7	2.6 ± 0.7
FEV ₁ , % predicted (mean ± SD)	67.4 ± 11.1	65.9 ± 11.7	66.8 ± 12.3
Reversibility, % (mean ± SD)	28.1 ± 13.2	29.8 ± 14.4	27.7 ± 14.5
Total daily β-agonist use (puffs)	5.6 ± 2.9	5.8 ± 2.9	5.7 ± 2.6

Both montelukast ($P = .002$) and beclomethasone ($P = .019$) reduced asthma flare-up compared with placebo. Rates of flare-up were 78%, 82.4%, and 91.9%, respectively.

Episodes of sustained asthma control

The percentage of patients receiving montelukast or beclomethasone with at least one episode of sustained asthma control were not significantly different ($P = .324$, Table II). Montelukast ($P = .039$) and beclomethasone ($P = .006$) were found to be significantly superior to placebo for this end point. The mean percentages of days of sustained asthma control were 33.4%, 32.1%, and 19.3% for patients taking montelukast, beclomethasone, and placebo, respectively. The percentage overlap for the distributions of days of sustained asthma control for the montelukast and beclomethasone groups was 100% (95% CI, 91.2%-100%).

Rescue corticosteroid use

The percentage of patients who used rescue corticosteroids was not significantly different between the montelukast and beclomethasone groups ($P = .473$, Table II). Compared with placebo, montelukast was significantly better with respect to the percentage of patients without rescue corticosteroid use ($P = .037$), whereas beclomethasone was not significantly different ($P = .127$).

Airway function (FEV₁)

Both montelukast and beclomethasone improved FEV₁ compared with placebo (0.14 L [$P = .004$] and 0.28 L [$P < .001$], respectively; Table II). The effect of beclomethasone was greater than that of montelukast (0.14 L difference, $P < .001$, Table II). The percentage overlap of the distributions of FEV₁ for the montelukast and beclomethasone groups was 81.1% (95% CI, 72.3%-90.0%; Fig 4).

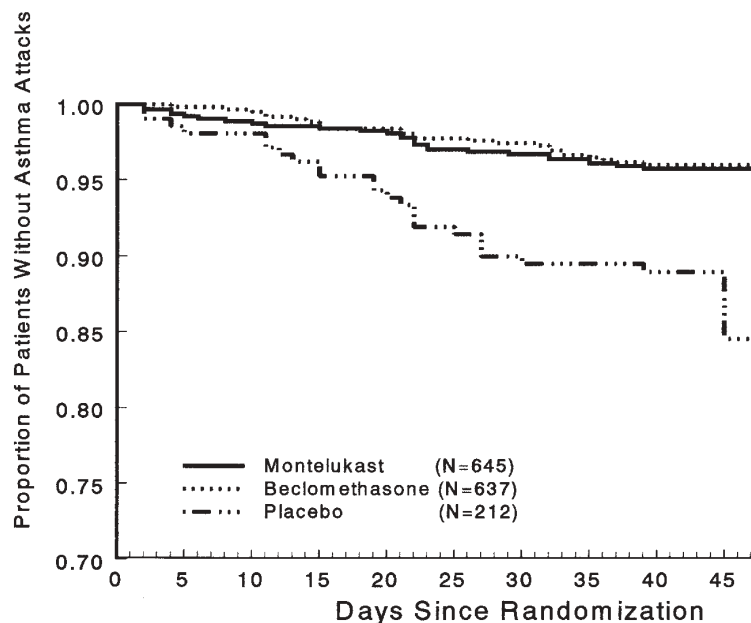


FIG 3. Time to first asthma attack during the 6-week treatment period. The cumulative percentage of patients without an asthma attack was estimated by using the Kaplan-Meier method. Time-to-event curves were compared between treatment groups by using a log-rank test (montelukast vs beclomethasone, $P = .487$; montelukast vs placebo, $P = .019$; beclomethasone vs placebo, $P = .081$).

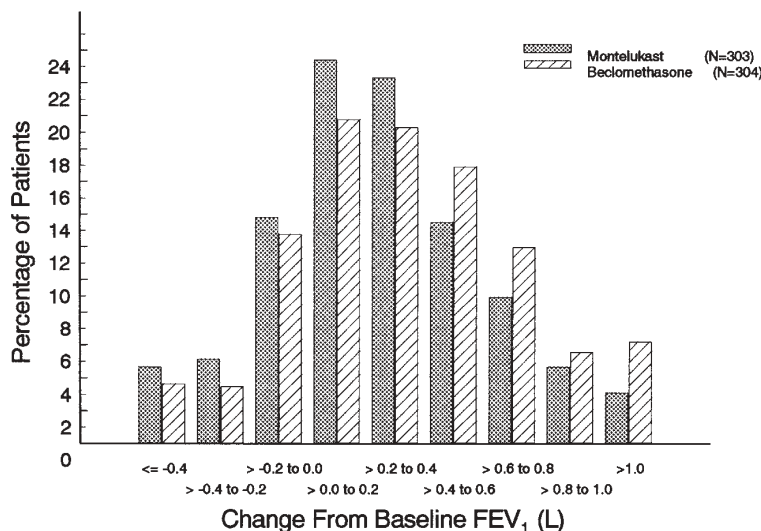


FIG 4. Frequency distributions of change from baseline FEV₁ (in liters) during the 6-week study for montelukast and beclomethasone. The overlap between montelukast and beclomethasone in the patient response distributions for change in FEV₁ was 81.1% (95% CI, 72.3-90.0).

Safety

Both montelukast and beclomethasone were generally well tolerated. The overall frequency of clinical adverse experiences was similar between the montelukast and beclomethasone groups. The most frequently reported adverse experiences (>5% of patients) included upper respiratory tract infection, headache, and

sinusitis, as well as asthma, and were not different among the treatment groups.

Of the 775 patients who had postbaseline laboratory tests, 13 (3.9%), 10 (3.0%), and 5 (4.5%) patients in the montelukast, beclomethasone, and placebo groups, respectively, experienced laboratory adverse experiences. There were no significant differences among the treatment groups in the frequency of laboratory abnormalities per sample.

TABLE II. Analysis of secondary end points

End point	Montelukast (n = 337)	Beclomethasone (n = 329)	Placebo (n = 111)
FEV ₁ , L (change from baseline)	0.24 ± 0.03*†	0.38 ± 0.03*	0.10 ± 0.04
Daily β-agonist use, puffs/d (% change from baseline)	-30.3 ± 2.4*	-31.9 ± 2.5*	-9.7 ± 4.0
Patients without an asthma attack, %	97.0 ± 0.9*	96.1 ± 1.1	91.9 ± 2.6
Patients without asthma flare-up, %	22.0 ± 2.3*	17.6 ± 2.1*	8.1 ± 2.6
Patients with at least 1 sustained asthma control episode, %	55.5 ± 2.7*	59.3 ± 2.7*	44.1 ± 4.7
Patients without rescue corticosteroid, %	97.3 ± 0.8*	96.4 ± 1.0	92.8 ± 2.5

Values are given as means ± SE.

**P* ≤ .05 versus placebo.†*P* ≤ .01 versus beclomethasone.

DISCUSSION

Although maintenance of airway function is an important feature of asthma control, optimizing airway function (eg, FEV₁) is not the sole objective of asthma therapy according to current National Asthma Education and Prevention Program and Global Initiative for Asthma treatment guidelines.^{1,20} In fact, current consensus guidelines suggest that even asthmatic patients with normal measures of airway function (FEV₁ >80% of the predicted value) who experience frequent symptoms of asthma should be treated with daily controller therapy.^{1,20} The present study was undertaken to determine the relative effect of an established first-line therapy for the treatment of persistent asthma, inhaled beclomethasone, compared with the leukotriene receptor antagonist montelukast. Both of these drugs have been shown to control asthma symptoms and improve airway function. The current study confirms the efficacy of both drugs compared with placebo and suggests that both are capable of improving asthma control for patients with persistent disease. Furthermore, it suggests that the clinical efficacy of the leukotriene receptor antagonist montelukast is underestimated by an index of airway caliber, such as FEV₁.

In the present study multiple clinical control indices were combined into a single end point, referred to as days of asthma control, to describe a desired and clinically recognized element of asthma control. The end point of days of asthma control incorporates elements that have been routinely measured in previous studies: daily albuterol use, nighttime awakenings, oral rescue corticosteroid use, and unscheduled medical care for the treatment of an asthma exacerbation.^{5,7} A day of asthma control represents a day in which a patient's asthma was well controlled, similar to the episode-free day described by Sculpher and Buxton.^{11,21} The latter was a measure proposed as a means of assessing effectiveness in a cost-effectiveness analysis. Such outcome measures are relevant to patients and prescribing physicians because they are quantifiable measures of the objectives of asthma treatment (controlling asthma and preventing asthma exacerbations).^{1,20}

As measured on the basis of this composite index and the individually incorporated elements, montelukast and

beclomethasone did not differ in the extent of clinical control achieved. Similarly, they did not differ in commonly measured indices of clinical effectiveness, such as reduction in β-agonist use or reduction in need for oral corticosteroids. Furthermore, they did not differ in the extent of sustained relief achieved.

Considering the apparent equivalence of beclomethasone and montelukast, as measured by the beneficial effects seen in the clinical indices, it might be surprising that these treatments differ in effects in airway function. It is recognized that airway caliber is an imperfect index of asthma control.²² In the current study beclomethasone might have a disproportionate effect on airway caliber compared with its effects on clinical outcomes. Conversely, with montelukast, asthma control might be underestimated by the degree to which pulmonary function improves. Although the pathobiology of this discrepancy is unclear, it suggests an important role for leukotrienes in mediating the acute deteriorations that lead to lack of control in asthma and is consistent with the finding that patients with asthma presenting to the emergency department have increased levels of leukotrienes.²³

Our results differ somewhat from those reported in a study comparing 88 μg twice daily of fluticasone with montelukast over 24 weeks.²⁴ In that study fluticasone produced more of an effect than montelukast on β-agonist use, symptoms, and rescue-free days. Interestingly, consonant with our findings, although FEV₁ improved more with fluticasone than with montelukast, there was not a significant difference in exacerbations between the 2 treatments. Whether the other differences noted are related to the use and dose of fluticasone, the length of the study, or differences in compliance between the different drug preparations across the studies is unclear. With regard to the latter point, it is noteworthy that compliance was not enforced in this study, and compliance with an inhaler might be worse than that with a tablet when compliance is not enforced.^{2,3} Thus the differences between inhaled corticosteroids and montelukast might diminish in studies that more closely approximate actual patient use.

In the present study neither treatment group achieved a high level of asthma control; however, the study's aim was to compare efficacy, not to explore therapeutic interven-

tions required to achieve full control. The doses of both beclomethasone and montelukast were fixed during the 6-week treatment period at a well-established and accepted initial starting dose (400 µg daily).^{1,20} Although this fixed-dose approach is commonly used to evaluate relative effects of therapies in a clinical research setting, it differs from clinical practice, in which prescribing physicians will adjust therapies and doses to achieve a desired level of control. Although it is possible to use higher doses of ICSs, there appears to be a relatively flat dose-response relationship for the efficacy of ICSs at greater than the dose used in this study.^{25,26} Furthermore, increased ICS absorption occurs with increased dose, which might lead to unwanted dose-related effects.²⁷⁻²⁹ In this context the combination of a leukotriene receptor antagonist and an inhaled corticosteroid have been shown to provide additional control⁶ and might be appropriate in patients whose symptoms are uncontrolled with either drug alone.

In conclusion, the current study demonstrates similar degrees of patient response to montelukast and beclomethasone when assessed by using broad and clinically relevant measurements of asthma control. It supports the use of montelukast as an effective initial alternative to inhaled controller therapies like inhaled beclomethasone for the treatment of chronic asthma. Furthermore, it suggests that ICSs, compared with leukotriene modifiers, might produce an effect on FEV₁ that is disproportionate to the clinical effect achieved. Therefore when identifying response to treatment, clinicians might need to put greater weight on clinical indices, as opposed to measurements of airway caliber.

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APPENDIX

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