

Oral Montelukast, Inhaled Beclomethasone, and Placebo for Chronic Asthma

A Randomized, Controlled Trial

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Background: Oral leukotriene receptor antagonists have been shown to have efficacy in chronic asthma.

Objective: To compare the clinical benefit of montelukast, a once-daily oral leukotriene receptor antagonist; placebo; and inhaled beclomethasone.

Design: Randomized, double-blind, double-dummy, placebo-controlled, parallel-group, 12-week study.

Setting: 36 sites worldwide.

Patients: 895 patients 15 to 85 years of age with chronic asthma and an FEV₁ 50% to 85% of predicted.

Interventions: Montelukast, 10 mg once daily at bedtime; inhaled beclomethasone, 200 µg twice daily, administered with a spacer device; or placebo.

Measurements: Primary end points were daytime asthma symptom score and FEV₁. Secondary end points were peak expiratory flow rates in the morning and evening, as-needed β-agonist use, nocturnal awakenings, asthma-specific quality of life, and worsening asthma episodes.

Results: Over the 12-week treatment period, the average percentage change from baseline in FEV₁ was 13.1% with beclomethasone, 7.4% with montelukast, and 0.7% with placebo ($P < 0.001$ for each active treatment compared with placebo; $P < 0.01$ for beclomethasone compared with montelukast). The average change from baseline in daytime symptom score was -0.62 for beclomethasone, -0.41 for montelukast, and -0.17 for placebo ($P < 0.001$ for each active treatment compared with placebo; $P < 0.01$ for beclomethasone compared with montelukast). Each agent improved peak expiratory flow rates and quality of life, reduced nocturnal awakenings and asthma attacks, increased the number of asthma-control days, and decreased the number of days with asthma exacerbations ($P < 0.001$ for each active treatment compared with placebo for each end point; $P < 0.01$ for beclomethasone compared with montelukast for each end point). Although beclomethasone had a greater mean clinical benefit than montelukast, montelukast had a faster onset of action and a greater initial effect. The two agents caused similar decreases in peripheral blood eosinophil counts ($P < 0.05$ for each agent compared with placebo). Both agents had tolerability profiles similar to that of placebo over the 12-week study.

Conclusions: Although beclomethasone had a larger mean effect than montelukast, both drugs provided clinical benefit to patients with chronic asthma. This finding is consistent with the use of these agents as controller medications for chronic asthma.

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For patients with persistent asthma, the National Asthma Education and Prevention Program recommends the regular use of “controller” medications to provide long-term control, together with as-needed use of “rescue” medications (1). Inhaled corticosteroids are currently the most commonly used controller medications (1). Although inhalation into the airway has advantages in terms of both safety and efficacy, problems with compliance with inhaled agents may limit their real-world effectiveness, especially in elderly and pediatric patients (2, 3).

Cysteinyl leukotrienes are important pro-inflammatory mediators of asthma (4). Recent clinical studies of leukotriene receptor antagonists (5–7) and a 5-lipoxygenase inhibitor (8) have shown these agents to have clinical benefit in patients with chronic asthma, and treatment guidelines now consider these agents alternative, first-line controller medications (1). Recent studies showed that montelukast, a potent and specific leukotriene receptor antagonist (9), had efficacy in adult (over a 12-week period) and pediatric (over an 8-week period) patient with chronic asthma and had a tolerability profile similar to that of placebo (10–12). To date, no comparisons of leukotriene receptor antagonists and inhaled corticosteroids have been published. Our placebo-controlled, parallel-group study, which was primarily designed to compare the effect of montelukast with that of placebo in a phase III

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clinical development trial, also compared montelukast and inhaled beclomethasone in patients with chronic asthma who require the daily use of a controller medication.

Methods

Patients

Healthy, nonsmoking, male and female patients 15 years of age and older were eligible to participate if they had had asthma for at least 1 year before the initial study evaluation. Each patient also had to have 1) an FEV₁ between 50% and 85% of predicted value, 2) an increase of at least 15% in absolute FEV₁ after the use of inhaled β -agonist on at least two of three visits during period 1 (see below), 3) a daytime asthma symptom score of at least 64 (of a possible 336), and 4) average daily use of at least one puff of as-needed, short-acting, inhaled β -agonist (salbutamol).

Patients were excluded from the study if they had used inhaled and oral corticosteroids, cromolyn, or nedocromil within 4 weeks before the initial evaluation; had used long-acting β -agonists, antimuscarinics, and newly instituted theophylline within 2 weeks before the initial evaluation; or had used long-acting antihistamines (for example, they could not have used astemizole within 3 months of the initial evaluation, and they could not have used terfenadine or loratadine within 2 weeks of the initial evaluation). Intermittent use of short-acting antihistamines was allowed, and immunotherapy was permitted if it had been started at least 6 months before the initial study evaluation and if the monthly dose remained constant.

Protocol

Our randomized, double-dummy, placebo-controlled, parallel-group trial had a 2-week, single-blind placebo run-in period (period 1); a 12-week, double-blind treatment period (period 2); and a 3-week, double-blind placebo washout period (period 3). Eligible patients were randomly assigned to one of three treatment regimens: 1) montelukast, 10 mg once daily in the evening; 2) inhaled beclomethasone, 200 μ g twice daily; or 3) placebo. The ratio of montelukast recipients to beclomethasone recipients to placebo recipients was 3:2:2, with a blocking factor of 7, according to a single, computer-generated allocation schedule. Patients, investigators, and coordinating center staff were blinded to the treatment schedule until all corrections to the database were completed.

During period 3, a subset of patients originally assigned to receive active treatment (approximately

40, as determined by the allocation schedule) was switched to placebo in a blinded manner. The other patients originally assigned to receive active treatment continued to receive that treatment. This allowed us to assess withdrawal from therapy.

The study was done at 36 clinical centers in 19 countries in Europe, Africa, Australia, Central America, and South America. The study protocol and informed consent were approved by local ethics review committees. All participants gave written informed consent before participation; consent of parents or guardians was obtained for patients younger than 18 years of age. Patients were recruited from the patient pool of each clinical study center and through local newspaper advertisements.

Medication

The study medication consisted of 10-mg montelukast film-coated tablets, placebo tablets that were identical in appearance to the montelukast tablets, beclomethasone (100 μ g/puff) in inhalers (Allen & Hanburys, Stockley Park, United Kingdom), and placebo in inhalers identical to those used for beclomethasone. Patients were instructed to take one tablet at bedtime and to take two puffs from the inhaler (using the AeroChamber spacer device [Clement Clark, Columbus, Ohio]) at bedtime and in the morning. Short-acting, inhaled β -agonist (salbutamol, 100 μ g/puff) (Allen & Hanburys) was to be used as needed.

Patients with worsening episodes of asthma that required additional therapy were treated with oral corticosteroids according to a standard protocol. Patients who had more than two worsening episodes of asthma requiring corticosteroid therapy were dropped from the study.

Measurements

Centralized spirometry training was done according to standard American Thoracic Society criteria before the start of the study. Spirometry was done at each visit after inhaled β -agonist therapy had been withheld for at least 6 hours, theophylline therapy had been withheld for at least 24 hours, and antihistamine therapy had been withheld for at least 48 hours. At least three spirometry maneuvers were done, and the largest FEV₁ was reported. Spirometry data were transmitted electronically to a central database and monitored continuously for quality, and feedback was given to the study centers (13). If quality was not maintained, sites were visited by coordinating center personnel.

Answers to four questions on daytime asthma symptoms and one question on nocturnal awakenings were collected on a daily diary card, as were morning and evening peak expiratory flow rate and daily use of as-needed salbutamol. With respect to

daytime asthma symptoms, patients used a 7-point scale (on which 0 means “best” and 6 means “worst”) to rate the severity of symptoms, their frequency, the degree to which they were bothersome, and their impact on daily activities. These ratings were combined into a mean daily score. Nocturnal awakenings were evaluated by the patient’s response (on a four-point scale) to a single question (14). The validation of these questions has been published elsewhere (14). Peak expiratory flow was measured in the morning and in the evening immediately before study medication was taken. The best of three measurements was recorded. Prespecified end points other than peak expiratory flow included peripheral blood eosinophil counts, global evaluations by physicians and patients (on a 7-point scale, on which 6 means “very much worse” and 0 means “very much better”) (7), and asthma-specific quality of life (15). Asthma outcome end points, including asthma attacks (defined as worsening asthma requiring oral corticosteroid treatment or an unscheduled visit to a physician, emergency department, or hospital), percentage of days with asthma exacerbations, and percentage of asthma-control days (as defined elsewhere [11, 16]), were also evaluated.

The diary card, the Asthma Quality-of-Life Questionnaire (15), and the global evaluation questions were translated from English into appropriate local languages and were validated for linguistic equivalence and cultural differences (17).

Patient compliance with study therapy was determined by weighing inhalers and counting tablets. The weight of a full canister was determined by averaging the weights of at least 50 canisters of beclomethasone and placebo. A standard puff weight was determined by repeatedly actuating and weighing 10 canisters.

Laboratory safety tests, including hematologic tests, serum biochemistry analysis, and urinalysis,

were done at prespecified visits, and the results were analyzed by a central laboratory. The central laboratory also determined eosinophil counts with an automated cell counter.

Statistical Analysis

Our primary objective was to compare montelukast with placebo with respect to two prespecified primary end points: FEV₁ and daytime symptom score. Other objectives were to compare beclomethasone with placebo and to compare montelukast with beclomethasone in a stepwise manner in accordance with the Dunnett–Tamhane approach, with the comparison of montelukast and beclomethasone prespecified as an estimation of the difference using 95% CIs (18). No multiplicity adjustments were made for each of the secondary end points, which were prespecified as supportive.

The analysis for each efficacy end point included all patients who had a measurement taken at baseline and at least one measurement taken after randomization. Treatment responses were calculated as the average change or percentage change from baseline to period 2; the baseline value was the average value for period 1.

With SAS software (SAS Institute, Inc., Cary, North Carolina), we used an analysis of variance (ANOVA) model to estimate treatment group means and between-group differences and to construct 95% CIs by using the least-square means and the differences in least-square means. The model contained factors for treatment, study center, and stratum (theophylline use). The consistency of the treatment effect across study centers, strata, and subgroups (which were formed according to sex, age, ethnicity, history of allergic rhinitis, and history of exercise-induced asthma) was assessed by interaction testing done using the ANOVA model with

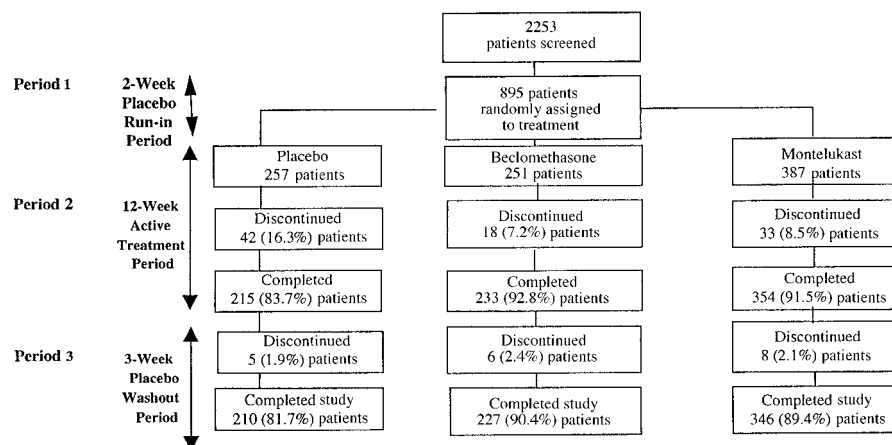


Figure 1. Trial profile. A total of 2253 patients were screened, and 895 were randomly assigned to study groups. The most common reason for exclusion was failure to meet the FEV₁ criteria (40% of excluded patients were excluded for this reason).

Table 1. Baseline Characteristics of Patients Randomly Assigned to Treatment

Characteristic	Placebo Group	Montelukast Group	Beclomethasone Group
Patients, <i>n</i>	257	387	251
Median age (range), <i>y</i>	36 (15–85)	35 (15–78)	35 (15–74)
Sex, %			
Male	43	40	35
Female	57	60	65
Ethnicity, %			
White	53	54	47
Hispanic	31	32	34
Other*	16	15	18
Theophylline users, %	10.5	10.3	9.6
History of allergic rhinitis, %	66	62	61
History of exercise-induced asthma, %	77	79	80
Median duration of asthma (range), <i>y</i>	18 (1–66)	17 (1–67)	18 (0.5–65)
Median smoking history (range), <i>pack-years</i>	0 (0–20)	0 (0–15)	0 (0–28)
Mean FEV ₁ ± SD, <i>L</i>	2.2 ± 0.7	2.2 ± 0.6	2.1 ± 0.6
Mean percentage of predicted value of FEV ₁ ± SD, %	66 ± 11	65 ± 10	65 ± 10
Mean morning peak expiratory flow rate ± SD, <i>L/min</i>	333 ± 99	339 ± 96	331 ± 97
Mean evening peak expiratory flow rate ± SD, <i>L/min</i>	354 ± 99	355 ± 102	348 ± 96
Mean daytime asthma symptom score ± SD†	2.4 ± 0.8	2.4 ± 0.9	2.4 ± 0.9
Mean β-agonist use ± SD, <i>puffs/d</i>	5.8 ± 3.9	5.4 ± 3.4	5.5 ± 4.2
Nocturnal awakenings ± SD, <i>nights/wk</i>	5.6 ± 1.5	5.5 ± 1.6	5.3 ± 1.7
Mean eosinophil count ± SD, <i>cells × 10³/μL</i>	0.35 ± 0.32	0.38 ± 0.38	0.35 ± 0.34
Mean pooled quality-of-life score ± SD†	3.15 ± 1.14	3.32 ± 1.10	3.16 ± 1.04

* Includes mestizo and other mixed ethnicities.

† On a scale from 0 to 6.

an interaction factor. The assumptions of the ANOVA model were assessed by the Shapiro–Wilk statistic for normality and by the Levene test for homogeneity of variances for the primary end points. The time to the first asthma attack was summarized by a Kaplan–Meier plot and was compared among treatments by using the log-rank test. All *P* values were rounded to three decimal places. To describe the distribution of response, we constructed a histogram of the percentage change from baseline in FEV₁.

We also analyzed the global patient and physician evaluations by collapsing the seven categories into three—better (0, 1, or 2), no change (3), and worse (4, 5, or 6)—and applying the Cochran–Mantel–Haenszel test.

Our study was designed to have 95% power ($\alpha = 0.05$, two-sided test) to detect an approximate difference of 6 percentage points in FEV₁ (percentage change from baseline) and an approximate difference of 10% in daytime symptom scores between montelukast and placebo, with 700 patients (300 in the montelukast group, 200 in the beclomethasone group, and 200 in the placebo group) completing period 2. (With moderate correlations [0.2 to 0.4] between FEV₁ and daytime symptom score, the power of the study to achieve the primary objective—determining significant improvement for both primary end points with montelukast compared with placebo—was 91%). More patients were prespecified for random assignment to montelukast treatment so that we could gain additional experience with the safety profile of montelukast.

Role of the Funding Source

Personnel from Merck Research Laboratories played a significant role in the design, conduct, monitoring, and analysis of the trial. The trial was conducted in accordance with guidelines for clinical trials of investigational agents established by worldwide regulatory authorities.

Results

A total of 895 patients (10.2% of whom were using concomitant theophylline therapy) were randomly assigned to treatment (**Figure 1**). Baseline characteristics were similar among the treatment groups (**Table 1**).

The percentage of patients who discontinued therapy during periods 2 and 3 was significantly larger in the placebo group (47 patients [18.3%]) than in the montelukast group (41 patients [10.6%]) or the beclomethasone group (24 patients [9.6%]) (**Figure 1**). Reasons for discontinuation included protocol deviations (16 placebo recipients [6%], 16 montelukast recipients [4%], and 10 beclomethasone recipients [4%]), withdrawal of consent (10 placebo recipients [4%], 11 montelukast recipients [3%], and 4 beclomethasone recipients [2%]), pregnancy (1 placebo recipient [0.4%], 2 montelukast recipients [0.5%], and 1 beclomethasone recipient [0.4%]), and loss to follow-up (9 placebo recipients [4%], 4 montelukast recipients [1%], and 4 beclomethasone recipients [2%]). In addition, 11 placebo recipients (4%), 8 montelukast recipients (2%), and 5 be-

clomethasone recipients (2%) discontinued therapy because of clinical adverse effects; worsening asthma was the most common of these effects (8 placebo recipients [3.1%], 4 montelukast recipients [1.0%], and 1 beclomethasone recipient [0.4%]). Other adverse events leading to discontinuation of therapy were menstruation disorder, eyelid edema, and pharyngeal discomfort (in the placebo group); epididymitis, urticaria, vasovagal reaction, and trauma (in the montelukast group); and rash, dyspepsia, neoplasm, and asthenia or fatigue (in the beclomethasone group).

Fifteen patients with significant protocol violations were excluded from the efficacy analysis before unblinding occurred. Furthermore, 10 patients lacked a baseline or a postallocation FEV₁ measurement and 19 patients lacked a baseline or postallocation daytime symptom score; these patients were excluded from analysis of these variables. The database was not unblinded during the course of the study.

Mean compliance (\pm SD) with the inhaled study medication during period 2 was 89.6% \pm 36.3% in the placebo group, 87.6% \pm 30.9% in the montelukast group, and 88.6% \pm 34.8% in the beclomethasone group. Mean compliance with the oral study medication during period 2 was 99.6% \pm 2.6% in the placebo group, 99.8% \pm 0.9% in the montelukast group, and 99.3% \pm 3.4% in the beclomethasone group.

Measurement of Airway Obstruction and Patient-Reported End Points

Compared with placebo, both montelukast and beclomethasone provided significant benefit with respect to FEV₁ (Figure 2), daytime symptom scores, and the secondary end points: as-needed β -agonist use, morning and evening peak expiratory flow rates, and nocturnal awakenings ($P < 0.001$) (Table 2). Beclomethasone had a larger mean effect than montelukast (Table 2). The mean differences between beclomethasone and montelukast were 5.8% (95% CI, 3.0% to 8.5%) for FEV₁, -0.21 (CI,

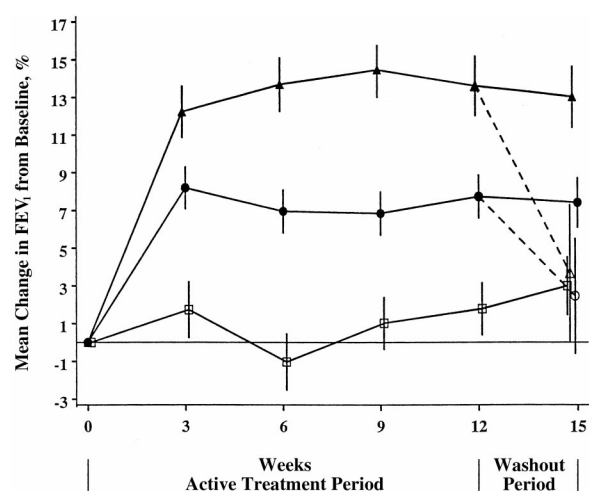


Figure 2. Mean percentage change from baseline (\pm SE) in FEV₁ over the 12-week treatment period. Black circles represent patients receiving montelukast, 10 mg once daily; black triangles represent patients receiving inhaled beclomethasone, 200 μ g twice daily; and squares represent patients receiving placebo. The dotted lines represent the treatment effect for the subsets of patients switched from active treatment to placebo (according to the initial allocation schedule) during the washout period. White circles represent patients switched from montelukast to placebo ($n = 52$); white triangles represent patients switched from beclomethasone to placebo ($n = 43$).

-0.33 to -0.09) for daytime symptom scores, -0.67 puffs/d (CI, -1.10 to -0.25 puffs/d) for β -agonist use, 15.3 L/min (CI, 8.1 to 22.5 L/min) for morning peak expiratory flow, 11.2 L/min (CI, 4.2 to 18.3 L/min) for evening peak expiratory flow, and -0.70 (CI, -1.08 to -0.32) for nocturnal awakenings.

The effect of FEV₁ was constant over the 12-week treatment period for both montelukast and beclomethasone (Figure 2). During the 3-week washout period (period 3), patients who were switched from montelukast or beclomethasone to placebo had their FEV₁ values return to baseline with no evidence of rebound worsening (Figure 2).

The FEV₁ response distribution for montelukast and beclomethasone is shown in Figure 3. Of the montelukast recipients, 42% had an improvement in FEV₁ of at least 11% from baseline (this was the median response of beclomethasone recipients; that is, 50% of beclomethasone recipients had an im-

Table 2. Primary and Other End Points*

End Point	Placebo Group	Montelukast Group†	Beclomethasone Group†
Percentage change from baseline in morning FEV ₁	0.7 (-2.3 to 3.7)	7.4 (4.6 to 10.1)	13.1 (10.1 to 16.2)
Change from baseline in daytime asthma symptom score	-0.17 (-0.30 to -0.05)	-0.41 (-0.53 to -0.29)	-0.62 (-0.75 to 0.49)
Percentage change from baseline in total daily β -agonist use	0.0 (-8.3 to 8.3)	-23.9 (-31.4 to -16.5)	-40.0 (-48.5 to -31.5)
Change from baseline in morning PEF, L/min	0.8 (-7.1 to 8.6)	23.8 (16.6 to 30.9)	39.1 (31.0 to 47.1)
Change from baseline in evening PEF, L/min	0.3 (-7.3 to 8.0)	20.8 (13.8 to 27.8)	32.1 (24.2 to 39.9)
Change from baseline in nocturnal awakenings, nights/wk‡	-0.5 (-0.9 to -0.1)	-1.7 (-2.07 to 1.3)	-2.4 (-2.8 to -2.0)
Change from baseline in eosinophil count, cells $\times 10^3/\mu$ L	-0.02 (-0.07 to 0.03)	-0.08 (-0.12 to -0.03)	-0.07 (-0.12 to -0.02)
Asthma attacks, %§	27.3	15.6	10.1

* Values given are the least-square mean (95% CI). PEF = peak expiratory flow rate.

† For all end points except eosinophil count, $P < 0.001$ compared with placebo. For eosinophil count, $P < 0.05$ compared with placebo.

‡ Patients with nocturnal asthma only (195 in the placebo group, 285 in the montelukast group, and 203 in the beclomethasone group).

§ Percentage of patients.

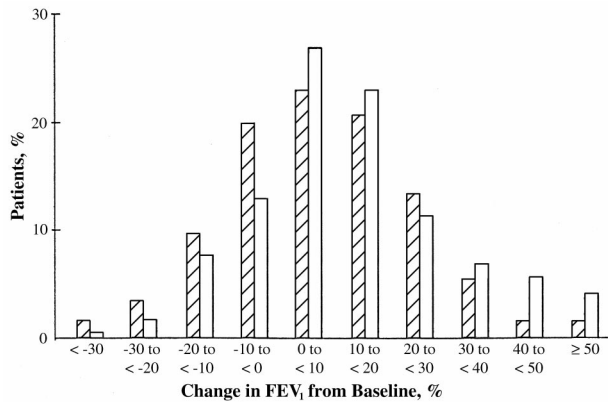


Figure 3. Distribution of treatment responses for FEV₁. The response distributions are shown as histograms for predefined intervals of percentage change in FEV₁. Striped bars represent patients receiving montelukast, 10 mg once daily; white bars represent patients receiving inhaled beclomethasone, 200 μg twice daily.

provement in FEV₁ of at least 11% from baseline). The proportions of patients who did not show an improvement in FEV₁ were 22% with beclomethasone and 34% with montelukast.

Montelukast had a faster and larger initial response than beclomethasone did; however, 7 to 10 days after therapy was initiated, the effect of beclomethasone surpassed that of montelukast (Figure 4). A similar response profile was observed with the other diary card variables, daytime asthma symptom scores, nocturnal asthma score, and as-needed use of β-agonist (data not shown).

No statistically significant ($P > 0.05$) treatment-by-subgroup interactions were seen. Within each treatment group, effects were consistent across baseline values of FEV₁, daytime symptom scores, as-needed β-agonist use, and peak expiratory flow rates.

Patients' global evaluations showed that 94.2% of beclomethasone recipients, 89.1% of montelukast recipients, and 73.4% of placebo recipients felt better after 12 weeks of treatment ($P < 0.001$ for each active treatment compared with placebo). Physicians' global evaluations showed similar results. Furthermore, improvements in the four quality-of-life domains—activity, symptoms, emotions, and environment—were significantly greater with montelukast and beclomethasone than with placebo ($P < 0.001$). The least-square mean improvements from baseline in the absolute score when the four domains were averaged was 0.83 (CI, 0.67 to 0.99) for beclomethasone recipients, 0.62 (CI, 0.48 to 0.77) for montelukast recipients, and 0.25 (CI, 0.09 to 0.41) for placebo recipients.

Worsening Episodes of Asthma

Patients receiving placebo, montelukast, and beclomethasone had asthma exacerbations on 26.1%, 15.2%, and 9.7% of days, respectively. The percent-

age of days with asthma exacerbations was decreased by 42% with montelukast compared with placebo and by 63% with beclomethasone compared with placebo ($P < 0.05$ for both comparisons). The percentage of asthma-control days was increased by 33% with montelukast and by 43% with beclomethasone compared with placebo (40.1%, 48.9%, and 27.4% of days were asthma-control days for montelukast, beclomethasone, and placebo recipients, respectively) ($P < 0.001$). Days with asthma exacerbations were less frequent and asthma-control days were more frequent in the beclomethasone group than in the montelukast group ($P < 0.05$).

Both montelukast and beclomethasone significantly reduced asthma attacks compared with placebo. The percentages of patients who had at least one asthma attack during the 12-week treatment period were 10.1% in the beclomethasone group, 15.6% in the montelukast group, and 27.3% in the placebo group. The protective effect of montelukast and beclomethasone against asthma attacks is shown in Figure 5. The effects of montelukast and beclomethasone did not differ significantly.

Blood Eosinophil Counts

Compared with placebo, montelukast and beclomethasone significantly and similarly decreased the peripheral blood eosinophil count over the 12-week treatment period ($P < 0.05$) (Table 2).

Safety

Clinical adverse effects that occurred in at least 6% of patients in any treatment group are shown in Table 3. Worsening asthma, headache, and upper respiratory tract infection were the most commonly reported clinical adverse effects. In all three treatment groups, clinical adverse effects were similar in frequency.

The incidence of laboratory adverse effects was similar in the three treatment groups. Of note, the

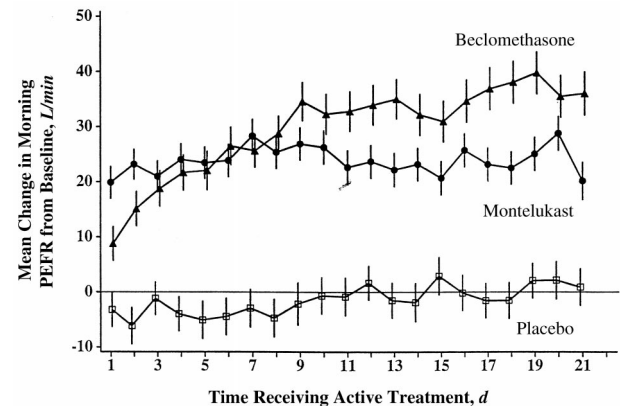


Figure 4. Onset of action of montelukast, beclomethasone, and placebo. Treatment effect for peak expiratory flow rate (PEFR) in the morning over the first 21 days of treatment. Vertical lines represent SEs.

Table 3. Incidence of the Most Common Clinical Adverse Effects and Alanine or Aspartate Aminotransferase Levels Greater Than the Upper Limit of Normal*

Variable	Placebo Group (n = 257)	Montelukast Group (n = 387)	Beclomethasone Group (n = 251)
	← n (%) →		
Worsening asthma	99 (39)	98 (25) [†]	48 (19) [†]
Headache	40 (16)	68 (18)	47 (19)
Upper respiratory tract infection	28 (11)	48 (12)	33 (13)
Influenza	10 (4)	25 (7)	17 (7)
Pharyngitis	11 (4)	25 (7)	16 (6)
ALT level > upper limit of normal [‡]	38 (15.0) [§]	53 (13.9) [§]	29 (11.6) [§]
ALT level > 3 times the upper limit of normal [‡]	2 (0.8)	3 (0.8)	3 (1.2)
AST level > upper limit of normal [‡]	14 (5.5) [§]	28 (7.3) [§]	15 (6.0) [§]
AST level > 3 times the upper limit of normal [‡]	2 (0.8)	1 (0.3)	4 (1.6)

* All clinical adverse effects with an incidence of 6% or more are shown. ALT = alanine aminotransferase; AST = aspartate aminotransferase.

[†] $P < 0.05$ for comparison with placebo by the Fisher exact test.

[‡] Percentages in this row are based on a total of 254 patients in the placebo group, 382 patients in the montelukast group, and 251 patients in the beclomethasone group.

[§] Patients with the highest level measured during periods 2 and 3.

percentages of patients with an alanine aminotransferase (ALT) or aspartate aminotransferase (AST) level more than three times the upper limit of normal were similar in the three groups (Table 3). All laboratory adverse effects, including elevated ALT and AST levels, were generally transient and self-limiting and did not result in discontinuation of therapy.

Discussion

Our study directly compared montelukast, a new oral leukotriene receptor antagonist, and beclomethasone, a commonly used inhaled corticosteroid. Although beclomethasone had a larger mean effect on many end points, both agents significantly improved asthma control, including the prevention of worsening episodes of asthma. Our data on the effect of montelukast is generally consistent with previously published data on other leukotriene modifiers (5–8). Recently updated guidelines (1) have positioned leukotriene receptor antagonists as an alternative to inhaled corticosteroids for some forms of persistent asthma.

The dose of montelukast used in our study was selected on the basis of previous dose-ranging studies (bedtime dosing was used in dose-selection studies to provide peak plasma concentrations during the characteristic worsening of asthma in the early morning). Dose-ranging studies of oral montelukast have shown that 10 mg given once daily is optimal; higher dosages have not been shown to provide greater clinically important mean benefit (10, 19,

20). However, titration studies investigating individual patient responses have not been done. The beclomethasone dosage used in our study, 200 μg given twice daily, is the initial dosage recommended in many national and multinational treatment guidelines (1). Whether higher dosages provide additional, clinically important mean benefit is controversial (21).

In our study sample with mild-to-moderate asthma, the distribution of responses to montelukast and beclomethasone were similar in pattern (unimodal) and largely overlapped (Figure 3). With each agent, some patients had little improvement and others had large improvements in FEV₁. These data do not support the hypothesis that response to antileukotriene agents can be used to easily separate patients into responder and nonresponder categories (22). Similar response distributions with inhaled beclomethasone and another leukotriene receptor antagonist have been reported in patients with mild asthma (23). In future studies of all antiasthma agents, it will be clinically useful to generate response distributions in many different patient groups (defined according to demographic characteristics and severity of asthma) to better understand how different patient populations respond to various therapies.

Improvement in asthma control and prevention of worsening episodes of asthma are the clinical goals of asthma therapy (1); therefore, the effect on clinical outcome of protection against worsening episodes of asthma is particularly important. Clinical research in asthma has been particularly hampered by a lack of data validating the relation of surrogate markers of asthma control (such as FEV₁) to clinical outcomes (such as prevention of asthma attacks) (24). In our clinical trial, both montelukast and inhaled beclomethasone gave similar protection against worsening episodes of asthma requiring use of oral corticosteroids, emergency department visits, or hospitalization.

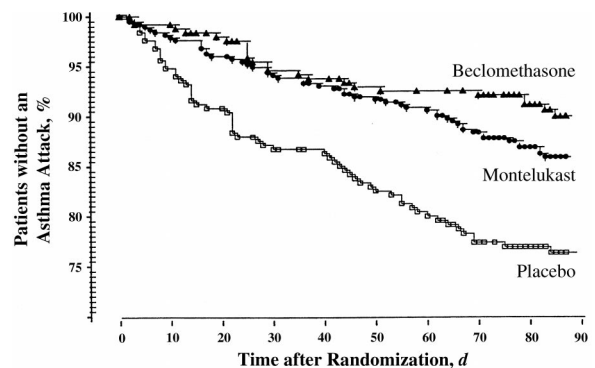


Figure 5. Time to first asthma attack. The proportion of patients without an asthma attack was estimated by using a Kaplan-Meier plot. $P = 0.006$ for montelukast compared with placebo; $P = 0.001$ for beclomethasone compared with placebo; and $P = 0.129$ for montelukast compared with beclomethasone.

The high compliance rate (>90%) seen with both montelukast and inhaled beclomethasone suggests that maximal efficacy responses were seen at the doses used in our study. Available data suggest that in clinical practice, oral therapies result in greater adherence (25). Because of differences in compliance with oral and inhaled therapy, it is important to consider the relative therapeutic effectiveness (in a pragmatic, real-world trial reflecting clinical practice) of each agent. Therefore, the design of our efficacy study has limitations: The long-term effects of the agents studied (especially in a real-world setting) is not investigated here. Although drop-out rates were low, incomplete data on each participant might have caused subtle survivor bias.

A comprehensive evaluation of the end points addressed by the daily diary cards (asthma symptoms, as-needed β -agonist use, and peak expiratory flow rates) showed that montelukast had its onset of action within the first day of therapy (this finding is consistent with findings in a previous clinical trial [11]) and had a greater average effect than beclomethasone during the first week of treatment (Figure 4), whereas the effect of beclomethasone became greater 7 to 10 days later. These observations suggest that the protection provided by montelukast and beclomethasone was generally similar over the first few weeks of therapy. During the 12-week treatment period, both montelukast and beclomethasone reached an efficacy plateau beyond which no further improvement was seen (Figure 2).

Discontinuation of both oral montelukast and inhaled beclomethasone therapy caused slow but clear decreases in effect. This suggests that over a 12-week treatment period, each agent may have reversible effects on some pathobiological process (such as mucosal edema or inflammatory cell recruitment). These discontinuation effects differ from those seen with inhaled corticosteroids in a patient population with milder asthma and a longer duration of treatment (26). In addition, after discontinuation of montelukast or beclomethasone therapy, our patients showed no evidence of rebound worsening of asthma. Certain agents, including some types of receptor antagonists, are known to cause rebound effects after discontinuation of therapy (27).

Beclomethasone and montelukast produced similar decreases in peripheral blood eosinophil counts (Table 2). It is hypothesized that the eosinophil is one of the most important effector cells of bronchial inflammation in asthma; this is suggested by the increased number of these cells and their products in the bronchi of patients with asthma (28). Bronchial biopsy studies have shown decreases in airway eosinophil counts in patients using inhaled corticosteroids (29), and a study of induced sputum showed

that montelukast also decreases airway eosinophil counts (30).

Montelukast and beclomethasone were generally well tolerated in our 12-week clinical trial: The incidence of clinical adverse effects with each active treatment was similar to that seen with placebo. Conflicting results about the long-term effects of corticosteroids (for example, cataracts or linear growth inhibition in children) have been reported (31, 32), and only limited experience with montelukast is available (33).

In conclusion, oral montelukast therapy has been shown to be effective in chronic asthma, producing significant improvements in FEV₁ and significant alleviation of daytime asthma symptoms. Although inhaled beclomethasone had a larger average effect than montelukast, montelukast had a more rapid initial response. The two agents each protected against worsening episodes of asthma.

Appendix

The following are members of the Montelukast/Beclomethasone Study Group: Ramiro Avila, MD (Portugal); Eric D. Bateman, MD (South Africa); Issahar Bendov, MD (Israel); Manuel Bernstein, MD (Venezuela); Wilfried Boehning, MD (Germany); Floriano Bonifazi, MD (Italy); Antero D. Palma Carlos, MD (Portugal); Alberto Cukier, MD (Brazil); Fernando DeBenedetto, MD (Italy); Waclaw Droszcz, MD (Poland); Fabian Galleguillos, MD (Chile); Rainer W. Hauck, MD (Germany); Jorge Hetzel, MD (Brazil); John Jordanoglou, MD (Greece); Carlos Jaramillo, MD (Colombia); Jose Roberto Jardim, MD (Brazil); Mordechai R. Kramer, MD (Israel); Gert Kunkel, MD (Germany); Jose Maria Olaguibel, MD (Spain); Hector J. Ortega, MD (Colombia); Rogelio Perez-Padilla, MD (Mexico); Cesar Picado-Valles, MD (Spain); Fernando H. Prieto, MD (Mexico); Reynaldo Quagliato, MD (Brazil); Gerhard Ras, MD (South Africa); Abe Rubinfeld, MD (Australia); Andrea Schulheim, MD (Austria); Nicolas Siafakas, MD (Greece); Tommaso Todisco, MD (Italy); Carlos Arturo Torres, MD (Colombia); Mario Vagliasindi, MD (Italy); Cesar Villaran, MD (Peru); Daniel Weiler-Ravell, MD (Israel); and Hartmut Zwick, MD (Austria).

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References

1. National Asthma Education and Prevention Program. Expert Panel Report II: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: U.S. Dept of Health and Human Services, National Institutes of Health; February 1997.
2. Dolovich M. Influence and inhalation technique on response and compliance. *European Respiratory Review*. 1995;5:166-9.
3. Newhouse MT. Aerosol therapy of asthma in adults and children: role of MDI, DPI, holding chambers and nebulizers. *Atemwegs-und-Lungenkrankheiten*. 1994;20(Suppl 5):268-76.
4. Lewis RA, Austen KF, Soberman RJ. Leukotriene and other products of the 5-lipoxygenase pathway. Biochemistry and relation to pathobiology in human diseases. *N Engl J Med*. 1990;323:645-55.
5. Spector SL, Smith LJ, Glass M. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D₄-receptor antagonist, in subjects with bronchial asthma. Accolate Asthma Trialists Group. *Am J Respir Crit Care Med*. 1994;150:618-23.
6. Grossman J, Faiferman I, Dubb JW, Tompson DJ, Busse W, Bronsky E, et al. Results of the first U.S. double-blind, placebo-controlled, multicenter clinical study with pranlukast, a novel leukotriene receptor antagonist. *J Asthma*. 1997;34:321-8.
7. Reiss TF, Altman LC, Chervinsky P, Bewtra A, Stricker WE, Noonan GP, et al. Effects of montelukast (MK-0476), a new potent cysteinyl leukotriene (LTD₄) receptor antagonist, in patients with chronic asthma. *J Allergy Clin Immunol*. 1996;98:528-34.
8. Israel E, Cohn J, Dubé L, Drazen JM. Effect of treatment with zileuton, a 5-lipoxygenase inhibitor, in patients with asthma. A randomized controlled trial. Zileuton Clinical Trial Group. *JAMA*. 1996;275:931-6.
9. Jones TR, Labelle M, Belley M, Champion E, Charette L, Evans J, et al. Pharmacology of montelukast sodium (Singulair), a potent and selective leukotriene D₄ receptor antagonist. *Can J Physiol Pharmacol*. 1995;73:191-201.
10. Altman LC, Munk Z, Seltzer J, Noonan N, Shingo S, Zhang J, et al. A placebo-controlled, dose-ranging study of montelukast, a cysteinyl leukotriene-receptor antagonist. Montelukast Asthma Study Group. *J Allergy Clin Immunol*. 1998;102:50-6.
11. Reiss TF, Chervinsky P, Dockhorn RJ, Shingo S, Seidenberg BC, Edwards TB. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma: a multicenter, randomized, double-blind trial. Montelukast Clinical Research Study Group. *Arch Intern Med*. 1998;158:1213-20.
12. Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, et al. Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. Pediatric Montelukast Study Group. *JAMA*. 1998;279:1181-6.
13. Botto A, Malmstrom K, Lu S, Zhang J, Reiss TF. Centralized spirometry quality control lowers the variability in multicenter asthma clinical trials [Abstract]. *Am J Respir Crit Care Med*. 1997;155:A893.
14. Santanello NC, Barber BL, Reiss TF, Friedman BS, Juniper EF, Zhang J. Measurement characteristics of two asthma symptom diary scales for use in clinical trials. *Eur Respir J*. 1997;10:646-51.
15. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax*. 1992;47:76-83.
16. Sculpher MJ, Buxton MJ. The episode-free day as a composite measure of effectiveness: an illustrative economic evaluation of formoterol versus salbutamol in asthma therapy. *Pharmacoeconomics*. 1993;4:345-52.
17. Guillemin F, Bombardier C, Beaton D. Cross-cultural adaptation of health-related quality of life measures: literature review and proposed guidelines. *J Clin Epidemiol*. 1993;46:1417-32.
18. Dunnett CW, Tamhane AC. Comparisons between a new drug and active and placebo controls in an efficacy clinical trial. *Stat Med*. 1992;11:1057-63.
19. Bronsky EA, Kemp JP, Zhang J, Guerreiro D, Reiss TF. Dose-related protection of exercise bronchoconstriction by montelukast, a cysteinyl leukotriene-receptor antagonist, at the end of a once-daily dosing interval. *Clin Pharmacol Ther*. 1997;62:556-61.
20. Noonan MJ, Chervinsky P, Brandon M, Zhang J, Kundu S, McBurney J, et al. Montelukast, a potent leukotriene receptor antagonist, causes dose-related improvements in chronic asthma. Montelukast Asthma Study Group. *Eur Respir J*. 1998;11:1232-9.
21. Kamada AK, Szefer SJ, Martin RJ, Boushey HA, Chinchilli VM, Drazen JM, et al. Issues in the use of inhaled glucocorticosteroids. The Asthma Clinical Research Network. *Am J Respir Crit Care Med*. 1996;153(6 Pt 1):1739-48.
22. In KH, Asano K, Beier D, Grobholz J, Finn PW, Silverman EK, et al. Naturally occurring mutations in the human 5-lipoxygenase gene promoter that modify transcription factor binding and reporter gene transcription. *J Clin Invest*. 1997;99:1130-7.
23. Laitinen LA, Naya IP, Binks S, Harris A. Comparative efficacy of zafirlukast and low dose steroids in asthmatics on prn β_2 -agonists [Abstract]. *Eur Respir J*. 1997;10:419s, P2716.
24. Alderman MH. Blood pressure management: individualized treatment based on absolute risk and the potential for benefit. *Ann Intern Med*. 1993;119:329-35.
25. Kelloway JS, Wyatt RA, Adlis SA. Comparison of patients' compliance with prescribed oral and inhaled asthma medications. *Arch Intern Med*. 1994;154:1349-52.
26. Haahela T, Jarvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med*. 1994;331:700-5.
27. Nattel S, Rangno RE, Van Loon G. Mechanism of propranolol withdrawal phenomena. *Circulation*. 1979;59:1158-64.
28. Bousquet J, Chané P, Vignola AM, Lacoste JY, Michel FB. Eosinophil inflammation in asthma. *Am J Respir Crit Care Med*. 1994;150:933-8.
29. Trigg CJ, Manolitsas ND, Wang J, Claderon MA, McAulay A, Jordan SE, et al. Placebo-controlled immunopathologic study of four months of inhaled corticosteroids in asthma. *Am J Respir Crit Care Med*. 1994;150:17-22.
30. Leff JA, Pizzichini E, Efthimiadis A, Boulet LP, Wei LX, Weinland DE, et al. Effect of montelukast (MK-0476) on airway eosinophilic inflammation in mildly uncontrolled asthma: a randomized placebo-controlled trial [Abstract]. *Am J Respir Crit Care Med*. 1997;155:A977.
31. Cumming RG, Mitchell P, Leeder SR. Use of inhaled corticosteroids and the risk of cataracts. *N Engl J Med*. 1997;337:8-14.
32. Agertoft L, Pedersen S. Effects of long-term treatment with an inhaled corticosteroid on growth and pulmonary function in asthmatic children. *Respir Med*. 1994;88:373-81.
33. Reiss TF, White R, Noonan G, Korenblat P, Hess J, Shingo S. Montelukast (MK-0476), a CysLT₁ receptor antagonist, improves the signs and symptoms of asthma over one year of treatment. Montelukast Study Group [Abstract]. *Eur Respir J*. 1997;10:437s, P2808.