A placebo-controlled, dose-ranging study of montelukast, a cysteinyl leukotriene–receptor antagonist

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Background: The cysteinyl leukotrienes are important mediators of bronchial asthma. The clinical effect of montelukast, a potent cysteinyl leukotriene–receptor antagonist, was investigated in a randomized, placebo-controlled, multicenter, parallel-group, dose-ranging study.
Methods: After a 3-week, single-blind, placebo run-in period, 343 asthmatic patients (FEV_1 40% to 80% of the predicted value with an improvement in FEV_1 of at least 15% [absolute value] after receiving inhaled β-agonists on at least two occasions) were randomly assigned to one of six treatment groups: placebo; 10, 100, or 200 mg once daily montelukast in the evening; or 10 or 50 mg twice daily montelukast for a 6-week, double-blind treatment period followed by a 1-week placebo washout period. All patients used inhaled, short-acting β-agonists as needed.
Results: All montelukast doses caused similar and significant differences compared with placebo in asthma control endpoints. The least-square mean difference between pooled montelukast groups and placebo in the percentage change from baseline in morning FEV_1 (10.30%; 95% CI: 5.56 to 15.04), as-needed β-agonist use (–0.98 puffs; 95% CI: –1.53 to –0.44), morning peak expiratory flow rate (18.80 L/min; 95% CI: 8.62 to 28.98), physicians' and patients' global evaluations, and asthma-specific quality-of-life scores were all significant ($p \leq 0.050$). The incidence of adverse experiences was not dose related and was similar between placebo and montelukast treatment.
Conclusion: Montelukast caused a significant improvement in chronic asthma at an oral, once daily evening dose as low as 10 mg. (J Allergy Clin Immunol 1998;102:50-6.)

Key words: *Asthma, cysteinyl leukotriene–receptor antagonist, montelukast*

Abbreviations used

ANOVA:	Analysis of variance
CI:	Confidence interval
CysLT:	Cysteinyl leukotriene receptor
LS:	Least squares
PEFR:	Peak expiratory flow rate

The cysteinyl leukotrienes (LTC_4, LTD_4, and LTE_4), collectively known as the slow-reacting substance of anaphylaxis, play an important role in asthma. They are released from proinflammatory cells, including eosinophils and mast cells, and appear to mediate many of the pathophysiologic processes associated with asthma, including bronchoconstriction,[1] mucus secretion,[2] and vascular permeability.[3]

The cysteinyl leukotrienes have been shown to be up to 1000 times more potent as bronchoconstrictors than histamine or methacholine in both normal and asthmatic subjects.[4] Present evidence suggests that the human lung contains two cysteinyl leukotriene receptors ($CysLT_1$ and $CysLT_2$). The presence of two receptors was identified by physiologic studies demonstrating the different response of isolated airways and isolated pulmonary veins to the inhibitory effects of leukotriene-receptor antagonists in the presence of constriction caused by LTD_4.[5] To date, these receptors have neither been isolated nor cloned.

Clinical trials with potent $CysLT_1$ antagonists have provided direct evidence for the involvement of cysteinyl leukotrienes in human asthma by demonstrating improvement in asthma control. Among these agents, montelukast (MK-0476), a competitive and specific $CysLT_1$ antagonist, is one of the most potent compounds. Competing against tritiated LTD_4 in human U937 cells in the presence of 1% human plasma, montelukast demonstrates a 50% receptor-inhibiting concentration of approximately 0.7 nmol/L.[6] Additionally, montelukast has been shown to provide potent and long-lasting antagonism (over a once daily dosing interval) of airway $CysLT_1$ in asthmatic patients.[7]

The objectives of the study reported here were (1) to determine whether montelukast can improve the signs and symptoms of chronic asthma over a 6-week treatment period, (2) to determine if montelukast causes a dose-related response between 10 to 200 mg per

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day, and (3) to determine the safety profile of montelukast over a 6-week treatment period.

METHODS

Patients

Healthy, nonsmoking (for longer than 1 year) patients with chronic asthma (men and women of nonchildbearing potential) 18 to 65 years of age were enrolled in the study. Eligible patients were required to demonstrate an FEV_1 between 40% and 80% of the predicted value (withholding short-acting, inhaled β_2-adrenergic agonist for 6 hours) and reversible airways obstruction (an increase in FEV_1 absolute value of 15% or greater) 20 to 30 minutes after inhalation of β–agonist at least twice each during the prestudy visit and run-in period. Additionally, a total asthma daytime symptom score of at least 40 per week (calculated from responses to a daytime diary, see below), and at least one puff per day of as-needed, inhaled, short-acting β-agonist during the last 2 weeks before randomization were needed. Patients were required to maintain their usual day/night, awake/sleep cycles. Female patients had a negative serum β-human chorionic gonadotropin test at the prestudy visit.

Patients were excluded for an active upper respiratory tract infection within 3 weeks, acute sinus disease requiring antibiotic therapy within 1 week, emergency room treatment for asthma within 1 month, or hospitalization for asthma within 3 months of the prestudy visit. Written informed consent, approved by the respective institutional review boards, was obtained from each patient.

Study design

This double-blind, randomized, three-period, parallel-group study comparing the clinical effect of five different treatments of montelukast to placebo was conducted at 30 study centers. There was a 3-week, single-blind, placebo run-in period (period I) followed by a 6-week active treatment period (period II), which was performed in a double-blind fashion. During active treatment, patients received (1) placebo twice daily; (2) placebo in the morning and 10, 100, or 200 mg once daily montelukast administered in the evening; or (3) 10 or 50 mg twice daily montelukast administered in the morning and evening according to a computer-generated allocation schedule. Patients returned to the study center for weekly evaluations. After completion of period II, patients entered a single-blind, 1-week placebo washout period (period III).

At each weekly visit, starting at visit 1, patients received four bottles (two in the morning and two in the evening) of study medication containing 10, 50, or 100 mg of montelukast or matching-image placebo capsules. Patients were instructed to take one capsule from each of the two morning bottles and one capsule from each of the two remaining bottles in the evening. Patients also received a Mini-Wright Peak Flow Meter (Clement Clark, Columbus, Ohio). The first dose of study medication in the active treatment period (taken from the evening bottles) was administered to the patient in the clinic, and serial spirometry measurements were performed (see below).

During the study, all patients used inhaled, short-acting β-agonist (albuterol, 90 μg/puff) on an as-needed basis. Additionally, twice daily theophylline and inhaled corticosteroids (at a constant dose and dosing interval beginning at least 1 and 2 weeks before the prestudy visit, respectively) were allowed in no more than 20% of patients. Also, short- and intermediate-acting antihistamines; cough suppressants, expectorants, and nasal decongestants in monosubstance formulations; nasal cromolyn; acetaminophen; codeine; estrogen; and thyroid hormone were permitted. Mild consumption of alcohol and caffeine maintained at a constant dose throughout the study was permitted. Patients were excluded from participation if they were taking oral corticosteroids within 1 month and inhaled, long-acting β-agonist and anticholinergic agents within 2 weeks of the prestudy visit.

Efficacy measurements

Morning spirometry (FEV_1) was performed during weekly clinic visits. Other clinic measurements performed included asthma-specific quality of life, physicians' and patients' global evaluations of asthma, and peripheral blood eosinophil counts. Measurements recorded by the patient at home on a daily diary card included morning (AM) and evening (PM) peak expiratory flow rates (PEFRs); symptoms, including daytime asthma symptoms and nocturnal awakenings; and as-needed β-agonist use.

Spirometry. Spirometry was performed weekly before the morning dose of study medication at 7 AM (±1 hour), approximately 12 hours after the previous evening dose of study medication. Inhaled β-agonist, theophylline, and short- and intermediate-acting antihistamines were withheld for 6, 24, and 48 hours, respectively, before each clinic visit. Inhaled corticosteroid doses were administered on arising, after measurement of peak flow, and not less than 1 hour before the morning clinic visit. β-Agonist reversibility (FEV_1 20 to 30 minutes after administration of two puffs of β-agonist [albuterol]) was determined before and 6 weeks after the randomization visit. Additionally, spirometry measurements were performed 1 and 2 hours after the clinic-administered first active-treatment period dose. A standard spirometer (Puritan-Bennett PB 100/PB110; Wilmington, Mass.) was used at all clinical centers. All spirometry measurements were reviewed centrally to ensure uniform adherence to American Thoracic Society[8] standards of acceptability and reproducibility. The largest FEV_1 from at least three acceptable maneuvers was recorded. When appropriate, feedback was given to individual clinical centers to enhance quality.

Diary card. The daily diary card included daytime symptoms (completed at bedtime) and nocturnal awakening (recorded in the morning upon awakening) scales previously shown to have acceptable evaluative measurement properties.[9] Additionally, the amount of as-needed β-agonist was recorded in the morning and evening as the number of puffs.

Peak expiratory flow rate. Peak flow was measured by the patient immediately upon arising in the morning (AM PEFR) and immediately before the evening dose of study medication (PM PEFR) after having withheld inhaled β-agonist for at least 4 hours. The best of at least three maneuvers was recorded on the diary card.

Global evaluations. On completing period II, both physicians and patients independently evaluated the overall change in asthma. The question, "Compared to when the patient (I) entered the study, the patient's (my) asthma is now," was answered on a 7-point scale. Responses included: "very much better," "moderately better," "a little better," "unchanged," "a little worse," "moderately worse," and "very much worse." When answering this question, the physician had access to the verbal history, physical examination results, and FEV_1 measurements. For the purpose of analysis, the three "better" and three "worse" categories were combined.

Asthma-specific quality-of-life questionnaire. The patient completed a validated, self-administered, quality-of-life questionnaire[10] at the randomization visit before receiving study medication and at the last visit of period II. The questionnaire was composed of four quality-of-life domains: activity, symptoms, emotions, and environment. In response to the questions, patients identified an answer on a 7-point scale, which ranged from 0 (worst) to 6 (best).

TABLE I. Randomized patients: Characteristics at baseline

		Montelukast				
	Placebo (*n* = 58)	**10 mg qd (*n* = 57)**	**10 mg bid (*n* = 54)**	**50 mg bid (*n* = 57)**	**100 mg qd (*n* = 56)**	**200 mg qd (*n* = 61)**
Median age, yrs (range)	36 (18-62)	33 (18-67)	33 (19-52)	40 (19-65)	37 (19-66)	39 (18-61)
Sex (%)						
M	78	79	78	74	70	77
F	22	21	22	26	30	23
Concomitant medication (stratum), (%)						
Inhaled corticosteroid	21	16	24	25	23	15
Theophylline	17	21	24	25	27	25
Inhaled steroid plus theophylline	4	11	7	5	14	12
β-agonist only	59	53	44	46	36	49
Baseline asthma measurements (mean [SD)])						
FEV_1 (L)	2.4 (0.7)	2.5 (0.7)	2.5 (0.7)	2.4 (0.8)	2.3 (0.7)	2.4 (0.8)
FEV_1 (% predicted)	59 (13)	62 (13)	62 (13)	60 (15)	61 (13)	61 (14)
Daytime symptoms (score)	2.6 (0.7)	2.5 (0.9)	2.7 (0.8)	2.5 (0.6)	2.6 (0.8)	2.5 (0.7)
β-agonist use (puffs/day)	5.3 (3.0)	5.0 (3.0)	5.0 (3.1)	5.6 (3.3)	4.7 (2.8)	5.1 (2.9)
AM PEFR (L/min)	397.6 (104.8)	415.6 (86.4)	414.4 (84.7)	408.6 (90.7)	400.3 (103.8)	395.0 (97.5)
Nocturnal awakenings (nights/week)	4.0 (2.4)	4.0 (2.5)	3.7 (2.8)	3.8 (2.5)	3.0 (2.5)	3.8 (2.8)

qd, Once daily; *bid,* twice daily.

Asthma exacerbation. Days with worsening asthma episodes (asthma exacerbation) were determined from predefined changes in patient-recorded diary card parameters: a decrease greater than 20% from baseline in AM PEFR, PEFR less than 180 L/min, an increase greater than 70% from baseline in β-agonist use (minimum increase, two puffs), an increase greater than 50% from baseline in symptom score, "awake all night" because of asthma, or an unscheduled visit to a doctor or hospital.

Blood eosinophils. Blood obtained every other week after randomization was analyzed for eosinophil counts by an automated cell counter in a central laboratory.

Safety evaluations

Clinical laboratory tests (hematology, serum chemistry, and urinalysis) were performed every other week after randomization. A complete physical examination and a 12-lead electrocardiogram were completed before and at the completion of study.

Statistical methods

Analysis. An intention-to-treat approach was used, including all patient endpoints with prerandomization baseline values (defined as the mean values during the placebo run-in period) and at least one treatment period measurement. For all endpoints, the average response (change from baseline or percent change from baseline) was compared among treatments by using an analysis of variance (ANOVA) model that included terms for treatment, study center, stratum (inhaled corticosteroids and theophylline use), and treatment-by-stratum interaction. Ordinal data were analyzed with the Cochran-Mantel-Haenszel test to corroborate the ANOVA results. Tukey's modified linear trend test (stepwise trend test)[11] was used to assess dose-response relationship. When no significant dose response was observed, all montelukast doses were combined in a post hoc comparison with placebo by using the same ANOVA model. FEV_1, daytime symptom scores, AM PEFR, and as-needed daily β-agonist use were prespecified as key endpoints.

A 95% confidence interval (CI) for mean change or percent change from baseline (within-group change) was calculated by using the least-squares (LS) mean, as was the 95% CI for the difference between pooled montelukast treatment groups versus the placebo group (between-group change). Assumptions of normality and homoscedasticity were assessed and not found to be violated. All statistical tests were two-tailed, and a p value of 0.050 or less was considered statistically significant. The ability of montelukast and a β-agonist to provide additive bronchodilation was determined by comparing the changes in post-β-agonist percent predicted FEV_1 before and after randomization between placebo and montelukast treatment.

All randomized patients were included in the safety evaluations. Fisher's exact test was used to provide post hoc comparisons of the frequency of clinical and laboratory adverse experiences among treatment groups.

Power and sample size. The study was designed with a sample size of 45 patients per treatment group to have 80% power to detect (at $\alpha = 0.050$, two-tailed test) a mean difference between treatment groups in FEV_1 of 11 percentage points in mean percent change from baseline.

RESULTS

Patients

Three hundred forty-three patients (285 receiving montelukast and 58 receiving placebo) entered the active, double-blind treatment period. Of these, 307 (90%) completed active treatment and 299 (87%) completed the placebo washout period. In general, discontinuations were more frequent in the placebo group (11 [19%]) than in the pooled montelukast group (33 [12%]). There were no clinically meaningful differences between the treatment groups in demographic parameters or baseline characteristics (Table I).

Efficacy

Key endpoints. All montelukast treatment regimens were similar in their effect on the four key endpoints. Compared with placebo, all montelukast treatment groups demonstrated a significant ($p < 0.050$) improve-

TABLE II. Active treatment period changes in AM FEV_1, daytime symptom score, β-agonist use, and AM peak flow

		Montelukast					
	Placebo	**10 mg qd**	**10 mg bid**	**50 mg bid**	**100 mg qd**	**200 mg qd**	**Pooled**
Morning FEV_1 (L)							
Mean % change	1.5	11.4*	12.6*	9.8*	12.7*	12.5*	11.8*
95% CI for mean	–2.9 to 5.9	7.2 to 15.6	8.5 to 16.7	5.9 to 13.8	8.8 to 16.7	8.5 to 16.4	10.0 to 13.7
Daytime symptoms (score)							
Mean change	–0.16	–0.33	–0.32	–0.34	–0.49	–0.27	–0.35
95% CI for mean	–0.34 to 0.02	–0.51 to –0.16	–0.49 to –0.15	–0.50 to –0.17	–0.66 to –0.33	–0.43 to –0.10	–0.43 to –0.27
β-Agonist use (puffs/day)							
Mean change	–0.1	–1.2*	–0.9*	–1.1*	–1.3*	–1.1*	–1.1*
95% CI for mean	–0.6 to 0.4	–1.6 to –0.7	–1.4 to –0.4	–1.5 to –0.6	–1.8 to –0.9	–1.5 to –0.6	–1.3 to –0.9
AM PEFR (L/min)							
Mean change	–1.4	11.0	14.8*	13.1*	24.6*	23.8*	17.4*
95% CI for mean	–10.7 to 8.0	2.0 to 19.9	6.0 to 23.5	4.6 to 21.5	16.1 to 33.1	15.3 to 32.2	13.4 to 21.4

Mean represents LS mean; 95% CI based on LS means.
qd, Once daily; *bid*, twice daily.
*$p < 0.050$ versus placebo on the basis of stepwise linear trend test.

ment in FEV_1 and a decrease in as-needed β-agonist use. Montelukast caused a nonstatistically significant decrease in daytime symptom scores compared with placebo (Table II).

A dose-related treatment effect was not observed (Table II). Therefore all five montelukast treatment groups were pooled to estimate the treatment effect with greater confidence. Fig. 1 demonstrates the pooled mean results for the four key endpoints over the 6-week active treatment and placebo washout period. Montelukast caused consistent effects without evidence of rebound worsening on blind withdrawal of therapy.

Other endpoints. No dose-related effect of montelukast was observed with PM PEFR measurements (performed at trough of the once daily dosing interval) or nocturnal awakenings, although the pooled treatment groups were significantly different from the placebo group (Table III). Additionally, montelukast demonstrated a nondose-related improvement in each of the four quality-of-life domains, with the most responsive being the symptoms domain, which was consistent with the observed trend in daytime symptom scores (Table IV). Global evaluations were also significantly ($p < 0.050$ as determined by Cochran-Mantel-Haenszel test) better than placebo evaluations in a nondose–related manner. For physicians' evaluation, montelukast caused 76.4%, 19.0%, and 4.6% of patients to feel better, no change, or worse, respectively; whereas placebo caused 42.9%, 46.9%, and 10.2% of patients to feel better, no change, or worse, respectively. For the patients' evaluation, montelukast caused 82.0%, 15.4%, and 2.6% of patients to feel better, no change, or worse, respectively; whereas placebo caused 56.3%, 27.1% and 16.7% of patients to feel better, no change, or worse, respectively.

Asthma exacerbations were significantly reduced with montelukast treatment compared with placebo. During active treatment, the mean percentages of days patients experienced asthma exacerbations were 7.4% for pooled montelukast groups and 16.1% for the placebo group (95% CI for difference: –13.93 to –3.46).

Montelukast caused rapid bronchodilation after the first clinic-administered dose. This effect was evident by the first measurement, 1 hour after dosing. The mean percentage change in FEV_1 at 1 and 2 hours after dosing were 10.8% and 17.5% for the pooled montelukast dosages as compared with the placebo responses of 4.69% and 5.1% (95% CI for the differences: 0.55 to 11.76 and 4.76 to 20.16).

Montelukast and inhaled, short-acting β-agonists had additive bronchodilation. The post-β-agonist percent predicted FEV_1 increased 2.9 percentage points (means: 79.6% to 82.5%) for the pooled montelukast groups compared with a decrease of 0.7 percentage points (means: 74.9% to 74.2%) in the placebo group after randomization. The 3.6% difference between placebo and pooled montelukast groups was significant (95% CI for difference: 0.73 to 6.41).

Montelukast caused a nonstatistically significant decrease in peripheral blood eosinophils compared with placebo. The mean change in eosinophil numbers (baseline values, 0.27 and $0.30 \times 10^3/\mu l$ for the pooled montelukast treatments and placebo, respectively) were $-0.05 \times 10^3/\mu l$ for the pooled montelukast groups and $-0.02 \times 10^3/\mu l$ for the placebo group (95% CI for the difference: –0.07 to 0.02). No changes in other leukocyte numbers were observed (data not shown).

In addition, the treatment effects were consistent across patients using concomitant theophylline, inhaled corticosteroids, or both (stratum interactions were not significant for any endpoint).

Safety

Headache and upper respiratory tract infection were the most frequently reported clinical adverse experiences. There were no dose-related clinical adverse expe-

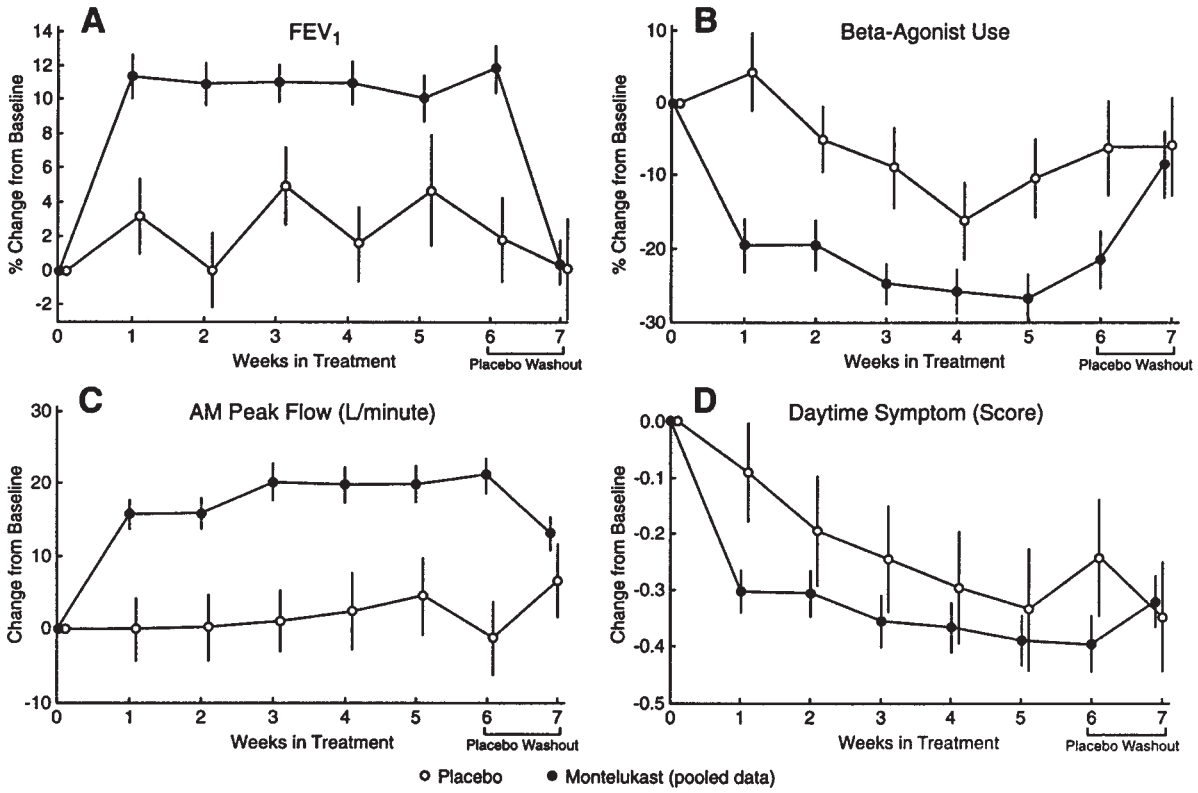

FIG. 1. Consistent effects of montelukast over active treatment period. Mean (± SEM) changes are shown for four key endpoints by using pooled montelukast treatment groups compared with placebo. **A,** Percentage change from baseline in morning FEV_1; **B,** β-agonist use percentage change from baseline; **C,** AM PEFR change from baseline; and **D,** daytime symptom score change from baseline (average of daytime symptom questions, 0 to 6 point scale each). Significant ($p < 0.050$) differences between the pooled montelukast groups compared with the placebo group were observed for average treatment period response for FEV_1, β-agonist use, and AM PEFR, but not for daytime symptom score. *Open circles,* Placebo; *filled circles,* pooled montelukast treatment groups.

riences among montelukast-treated patients, and there were no differences between the pooled montelukast treatment groups and the placebo group in the incidence of adverse events. Laboratory adverse experiences were more frequent in the placebo group (6.9%) than in the pooled montelukast group (3.2%). No patient discontinued because of a laboratory adverse experience. Adverse experiences with montelukast treatment were infrequent, transient, and self-limited.

DISCUSSION

Montelukast improved asthma control over a 6-week treatment period; however, a relationship between daily dose of montelukast (10 to 200 mg), dosing interval (once daily versus twice daily), and clinical efficacy parameters was not observed in this study. The similarity of response between once daily and twice daily administration and the persistent effect throughout the once daily dosing regimen demonstrated that twice daily dosing provided no additional benefit to that of once daily administration.

A dose-response relationship has been difficult to demonstrate for antiinflammatory asthma treatments. For example, dose-response studies with inhaled corticosteroids have demonstrated minimal dose-related effects.[12] In some instances larger metaanalyses were necessary to demonstrate dose-response effects that individual studies did not have the power to demonstrate.[13] Similarly, studies of other compounds, including leukotriene blockers, have not shown dose-related responses.[14] At least two explanations for the lack of dose response are possible in this study with montelukast. First, the doses investigated in this study were at the plateau (i.e., the top) of the dose-response relationship. Second, the dose-response relationship is shallow, and thus the distribution among the doses was insufficient to distinguish a difference in response. The latter possibility is less likely considering the 20-fold range of doses used in this study. To clarify the dose-response relationship, additional dose-response studies with doses lower than those in this trial will be necessary.

Over the 6-week treatment period, average weekly measurements of airway obstruction (FEV_1 measured 10 to 12 hours after dosing) were significantly improved in patients receiving montelukast compared with those receiving placebo. Additionally, montelukast caused bronchodilation within 60 minutes of a witnessed oral

TABLE III. Active treatment period changes in PM PEFR and nocturnal awakenings

		Montelukast					
	Placebo	**10 mg qd**	**10 mg bid**	**50 mg bid**	**100 mg qd**	**200 mg qd**	**Pooled**
PM PEFR (L/min)							
Mean change	–0.0	12.3*	7.7	12.6*	18.0*	18.5*	13.8*
95% CI for mean	–8.2 to 8.1	4.5 to 20.1	0.1 to 15.3	5.2 to 20.0	10.6 to 25.3	11.2 to 25.8	10.3 to 17.3
Nocturnal awakenings (nights/week)†							
Mean change	–0.8	–1.4	–1.7	–0.9	–1.8	–1.8	–1.5*
95% CI for mean	–1.4 to –0.1	–2.1 to –0.8	–2.5 to –1.0	–1.5 to –1.0	–2.5 to –1.2	–2.6 to –1.0	1.9 to –1.2

Mean represents LS mean; 95% CI based on LS means.
qd, Once daily; *bid*, twice daily.
*$p < 0.010$ versus placebo on the basis of stepwise linear trend test.
†In patients who had at least 2 nights per week of awakenings during the run-in period.

TABLE IV. Asthma-specific quality of life*

	Baseline	**Treatment**	**Change from baseline†**
Symptom domain			
Montelukast+	3.54	4.14	0.60‡
Placebo	3.33	3.53	0.17
Activity domain			
Montelukast+	4.02	4.42	0.38‡
Placebo	4.08	4.32	0.23
Emotion domain			
Montelukast+	3.57	4.09	0.50‡
Placebo	3.17	3.53	0.30
Environment domain			
Montelukast+	3.80	4.26	0.44
Placebo	3.67	3.98	0.34

*Seven point scale (0 to 6).
†Pooled treatment groups.
‡$p < 0.05$ compared with placebo.

dose. Montelukast, compared with placebo, added to the bronchodilation caused by the administration of inhaled, short acting β-agonist. This observation is consistent with results of previous studies of leukotriene receptor antagonists in which rapid bronchodilation[15] and additive effects with β-agonists were also noted.[16,17]

Improvement in patient-reported outcomes is an important goal of antiasthma therapy.[18] In this study montelukast caused significant decreases in patient-reported β-agonist use. Nocturnal awakenings and daytime symptom scores each improved with montelukast compared with placebo, although not significantly. However, a significant improvement was observed in the symptom domain of the asthma-specific quality-of-life questionnaire, providing evidence that montelukast improves asthma symptoms. The mean changes caused by montelukast in the asthma-specific quality-of-life symptom domain achieves the clinically significant magnitude previously described (≥0.5).[19]

A large placebo response was observed with daytime symptom scores. This unexplained response was not observed with other endpoints. This observation may be potentially explained by an overreporting of symptoms during the prerandomization (baseline) period to assure qualification for allocation. An overreporting of symptoms would cause regression to the mean during the treatment period, tending to minimize the differences between treatments.

An additional important goal of asthma therapy is the prevention of worsening asthma.[20] Worsening asthma has been variously defined in the literature, ranging from a mild worsening of signs and symptoms to hospitalization.[21] This endpoint *(exacerbations)*, including specific changes in diary card parameters, quantified important day-to-day worsening of asthma. Compared with placebo, montelukast protected against the occurrence of asthma exacerbations.

Present theories of asthma pathobiology suggest that the disease is a syndrome of inflammation characterized in part by increased numbers of eosinophils in the blood, which, with other inflammatory cells, infiltrate into the airways.[22] Measurement of peripheral blood eosinophils over the 6-week treatment period demonstrated that montelukast caused a nonstatistically significant decrease in eosinophils without affecting other leukocyte numbers. This observation raises the possibility that leukotriene receptor antagonists, such as montelukast, may have effects on some parameters of asthmatic inflammation. Cysteinyl leukotrienes have been shown to enhance proliferation of bone marrow eosinophil/basophil precursors[23] and to attract eosinophils into the lung.[24]

In summary, this trial demonstrates that montelukast administered once daily in the evening over a 6-week treatment period provides clinical benefit to patients with chronic asthma. A relationship between dose (and dosage interval) and clinical efficacy was not evident. At all doses studied (10 to 200 mg/day), montelukast was generally well tolerated without important clinical or laboratory adverse experiences. Further trials investigating the effect of once daily doses lower than 10 mg will be necessary to identify a dose-related response.

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REFERENCES

1. Dahlen SE, Hedquist P, Hammerstrom S, Samuelsson B. Leukotrienes are potent constrictors of human bronchi. Nature 1980;288:484–6.
2. Marom Z, Shelhamer JH, Bach MK, Morton DR, Kaliner M. Slow-reacting substances, leukotrienes C_4 and D_4, increase the release of mucus from human airways in vitro. Am Rev Respir Dis 1982;126:449–51.
3. Woodward DF, Wichmann BF, Gill CA, Wassermann MA. The effect of synthetic leukotrienes on tracheal microvascular permeability. Prostaglandins 1983;25:131–42.
4. Drazen JM, Austen KF. Leukotrienes and airway responses. Am Rev Respir Dis 1987;136:985-98.
5. Labat C, Ortiz JL, Norel X, Gorenne I, Verley J, Abrams TS, et al. A second cysteinyl leukotriene receptor in human lung. J Pharmacol Exp Ther 1992;263:800-5.
6. Jones TR, Labelle M, Belley M, Champion E, Charette L, Evans J, Ford-Hutchinson AW, et al. Pharmacology of montelukast sodium (SINGULAIR), a potent and selective leukotriene D_4-receptor antagonist. Can J Physiol Pharmacol 1995;73:191–201.
7. DeLepeleire I, Reiss TF, Rochette F,Botto A, Zhang J, Kundu S, et al. Montelukast causes prolonged, potent leukotriene D_4-receptor antagonism in the airways of patients with asthma. Clin Pharmacol Ther 1997;61:83-92.
8. Crapo RO, Hankinson JL, Irvin C. Standardization of spirometry. Am J Respir Crit Care Med 1995;152:1107-36.
9. 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.
10. 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.
11. Tukey JW, Ciminera JL, Heyse JF. Testing the statistical certainty of a response to increasing doses of a drug. Biometrics 1985;41:295-301.
12. Chervinsky P, van As A, Bronsky EA, Dockhorn R, Noonan M, LaForce C, et al. Fluticasone propionate aerosol for the treatment of adults with mild to moderate asthma. J Allergy Clin Immunol 1994;94:676-83.
13. Toogood JH. High-dose inhaled steroid therapy for asthma. J Allergy Clin Immunol 1989;83:528-36.
14. Spector SL, Smith LJ, Glass M, and the ACCOLATE Asthma Trialists Group. Effects of 6 weeks of therapy with oral doses of ICI 204,219, a leukotriene D_4 receptor antagonist, in subjects with bronchial asthma. Am J Respir Crit Care Med 1994;150:618-23.
15. Impens N, Reiss TF, Teahan JA, Desmet M, Rossing TH, Shingo S, et al. Acute bronchodilation with an intravenously administered leukotriene D_4 antagonist, MK-679. Am Rev Respir Dis 1993;147:1442-6.
16. Gaddy NJ, Margolskee DJ, Bush RK, Williams VC, Busse WW. Bronchodilation with a potent and selective leukotriene D_4 (LTD_4) receptor antagonist (MK-571) in patients with asthma. Am Rev Respir Dis 1992;146:358-63.
17. Hui KP, Barnes NC. Lung function improvement in asthma with a cysteinyl leukotriene receptor antagonist. Lancet 1991;337:1062-3.
18. U.S. Department of Health and Human Services. National Asthma Education Program, Expert Panel Report. Guidelines for the diagnosis and management of asthma. Bethesda (MD): National Heart, Lung, and Blood Institute; 1992; Publication No. 91–3042.
19. Juniper EF, Guyatt GH, Willan A, Griffith LE. Determining a minimal important change in a disease-specific quality of life questionnaire. J Clin Epidemiol 1994;47:81-7.
20. U.S. Department of Health and Human Services. National Heart, Lung, and Blood Institute/World Health Organization Workshop Report. Global initiative for asthma: global strategy for asthma management and prevention. Bethesda (MD): National Heart, Lung, and Blood Institute, National Institutes of Health; 1995; Publication No. 95–3659.
21. Taylor DR, Sears MR, Herbison GP, Flannery EM, Print CG, Lake DC, et al. Regular inhaled β-agonist in asthma: effects on exacerbations and lung function. Thorax 1993;48:134-8.
22. Bousquet JP, Chanez JY, Lacoste G, Barnéon G, Ghavanian N, Exander I, et al. Eosinophilic inflammation in asthma. N Engl J Med 1990;323:1033–9.
23. Wickremasingh RG, Khan MA, Hoffbrand AV. Do leukotrienes play a role in the regulation of proliferation of normal and leukemic hemopoietic cells? Prostaglandins Leukot Essent Fatty Acids 1993;48:123-6.
24. Laitinen L, Laitinen A, Haahtela T, Vilkka V, Spur BW, Lee TH. Leukotriene E_4 and granulocytic infiltration into asthmatic airways. Lancet 1993;341:989-90.