

Effects of montelukast (MK-0476), a new potent cysteinyl leukotriene (LTD₄) receptor antagonist, in patients with chronic asthma

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Background: Cysteinyl leukotrienes mediate signs and symptoms of asthma. In a double-blind, placebo-controlled, crossover study, a new potent and specific cysteinyl leukotriene (LTD₄) receptor antagonist, montelukast (MK-0476), was evaluated for tolerability and clinical efficacy in patients with chronic asthma (receiving and not receiving inhaled corticosteroids).

Methods: Twenty-nine nonsmoking patients with asthma (15 treated concomitantly with inhaled corticosteroids) with FEV₁ percent predicted values between 50% to 80% received MK-0476, 200 mg, or placebo three times daily for 10½ days (31 doses) in a random, crossover manner, after a 2-week, open, baseline period. Comparisons in FEV₁ (mean percent change from baseline after the first and last dose), mean daily daytime asthma and nocturnal awakening scores, and mean daily β-agonist use were made between treatment periods.

Results: Montelukast, compared with placebo, caused improvements in FEV₁ (mean percentage point difference of the percentage change from baseline) 3 and 4 hours after dosing on day 1 (hour 3, 9.0%; 95% confidence interval [CI] 0.53, 18.72; hour four, 10.9%; 95% CI - 0.25, 20.20) and day 11 (hour 3, 14.0%; 95% CI 0.76, 31.43; hour 4, 13.4%; 95% CI 1.24, 28.83). Reductions were observed in mean daily β-agonist use (1.0 puff/day [95% CI -1.61, -0.26]), mean daytime symptom scores, and nocturnal awakenings over the 10½ day treatment period. There were no important differences between the groups receiving and those not receiving inhaled corticosteroids. Montelukast was well tolerated with no serious clinical adverse events reported.

Conclusions: In this study Montelukast, 200 mg, administered three times daily for 10½ days, compared with placebo, was generally well tolerated and resulted in significant improvement in chronic asthma, irrespective of the presence of inhaled corticosteroids. (*J Allergy Clin Immunol* 1996;98:528-34.)

Key words: Montelukast (MK-0476), bronchodilation, cysteinyl leukotriene receptor antagonist

Approximately 5% of the worldwide population have asthma.¹ This prevalent clinical syndrome has been associated with cellular inflammation of the airways; the cysteinyl leukotrienes C₄, D₄, and E₄,

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Abbreviations used

ANOVA:	Analysis of variance
CI:	Confidence interval
CysLT ₁ :	Cysteinyl leukotriene ₁
LT:	Leukotriene

which are released from inflammatory cells (e.g., eosinophils or mast cells), appear to mediate many of the pathophysiologic processes associated with asthma including mucus production, decreased mucociliary clearance, changes in vascular permeability, and smooth muscle contraction.²⁻⁴

Clinical evidence for the involvement of leukotrienes in asthma has been obtained from trials with potent cysteinyl leukotriene₁ (CysLT₁) recep-

tor antagonists.⁵⁻¹⁰ Montelukast, a new investigational CysLT₁ receptor antagonist,¹¹ is one of the most potent antagonists; competing against tritiated LTD₄ for the receptors in guinea pig lung membranes in the presence of 1% human plasma, montelukast demonstrates a 50% inhibitory concentration of approximately 0.5 nmol/L.¹¹

The objective of this first multiple-day administration of oral montelukast was to evaluate the clinical benefit and the tolerability profile of this investigational agent in patients with mild-to-moderate chronic asthma. To identify any multiple-dose tolerability limitations to the administration of montelukast, a daily dose (200 mg three times daily, well above that required to provide physiologic blockade of airway LTD₄ receptors¹²) was administered to the study participants¹² for 10½ days. Further, to determine the effect of concomitant inhaled corticosteroid therapy on efficacy and tolerability parameters, patients receiving and not receiving concomitant inhaled corticosteroid therapy were enrolled in this study.

METHODS

Patients

Nonsmoking (at least 1 year, having smoked no more than 5 pack-years) male and female (without childbearing potential) patients between 18 and 55 years of age (within 15% of ideal body weight) with a history of recurring symptoms associated with asthma including dyspnea, wheezing, or cough requiring treatment for at least 1 year were eligible for study participation. Patients admitted to the study were required to have reversible airway obstruction (defined as an FEV₁ between 50% and 80% of predicted normal values and an increase of at least 15% in the absolute value of FEV₁ within 30 minutes after inhalation of 2 puffs [180 µg] of albuterol on at least two of the three prerandomization visits). The study design allowed approximately 50% of enrolled patients to receive concurrent inhaled corticosteroid therapy; the daily dose of this therapy remained constant for at least 1 month before and throughout the study period. In the 4 weeks before the prestudy visit, patients had no symptoms of an upper respiratory tract infection and had not participated in another clinical trial. Patients were in good health (free of concomitant illness) as assessed by history, physical examination, and laboratory data. A chest radiograph obtained within 12 months before the study initiation showed no evidence of infectious, oncologic, or other active pulmonary disease. Patients were excluded from study participation if they had received long-acting antihistamines (within 3 months), inhaled cromolyn (2 weeks), oral or intravenous corticosteroids (1 month), or oral β-agonists (2 weeks). Additionally, patients had to demonstrate the ability to perform acceptable, reproducible spirometry

measurements. Written informed consent, reviewed and approved by the respective institutional review boards, was obtained from each patient before study initiation.

Study design

This multicenter study had a double-blind, randomized, placebo-controlled, two-period crossover design; a 2-week open, baseline period preceded the blind periods. To determine eligibility, patients were evaluated approximately 1 week before beginning the baseline period. At this visit, a complete physical examination, including 12-lead electrocardiogram, chest x-ray (if necessary), and spirometry were performed. Blood (chemistry and hematology) and urine samples, collected for laboratory safety assessment, had to be free of clinically important abnormalities before a patient was allowed to enter the baseline period.

During the prerandomization baseline period, patients were asked to return to the clinic at weekly intervals. During this period, patients were assessed for their ability to comply with study procedures, achieve spirometry and asthma symptom inclusion criteria (based on a daily asthma diary), and establish baseline values for comparison with treatment periods. Neither montelukast nor placebo was administered during this baseline period.

Patients meeting clinical requirements during this prerandomization baseline period entered the double-blind, crossover portion of this study. After receiving an allocation number from a computer-generated, randomized schedule, patients received 31 doses of either montelukast, 200 mg, or placebo (administered three times daily for 10½ days) in each of two separate periods. All morning doses were administered in the clinic under observation; additionally, the first and last doses (on days 1 and 11) of each period were followed by serial measurements of spirometry (up to 12 hours after the dose was given).

All doses of study medication were administered with water at least 1 hour before or 3 hours after any meal. The following medications were withheld before each measurement of spirometry: short-to-intermediate-acting antihistamines (48 hours), inhaled β-agonists (6 hours), and inhaled corticosteroids (1 hour). Alcohol consumption was forbidden for 24 hours before the prestudy visit and throughout both study periods. Use of caffeine products was not permitted for 8 hours before all spirometry measurements or for 12 hours after the first and last doses of each treatment period. An interval of at least 48 hours occurred between treatment periods.

Patients received the first dose of the assigned oral study drug in each treatment period at approximately 8:00 AM; spirometry measurements were performed 30 and 15 minutes before the administration of the first observed dose and 3 and 4 hours after dosing. Patients were discharged from the clinic with instructions regarding administration of the study medication and completion of the daily asthma diary cards (daytime asthma

TABLE I. Patient demographics

Patient No.	Sex	Age (yr)	Weight (lb)	Height (inches)	Pre-albuterol* FEV ₁ (L)	FEV ₁ (% predicted)	Asthma medication† (total daily dose)
1	M	34	188	75	2.32	50	Triam (12 puffs)
2	M	28	145	64	1.90	49	Triam (4 puffs)
3	M	34	185	71	3.42	77	Triam (4 puffs)
4	M	44	212	72	1.90	52	Triam (3 puffs)
5	M	31	164	67	2.40	69	Beclo (4 puffs)
6	M	19	195	74	2.99	58	—
7	M	23	170	70	3.46	75	—
8	F	41	164	68	2.07	63	—
9‡	M	27	165	68	3.46	80	—
10	M	54	174	69	1.98	53	—
11	F	46	150	66	1.94	64	Triam (8 puffs)
12‡	M	26	175	69	2.48	56	Beclo (9 puffs)
13	M	21	188	70	2.82	61	Beclo (9 puffs)
14	M	28	208	72	3.55	76	Triam (6 puffs)
15	M	34	150	68	2.57	62	Beclo (6 puffs)
16	M	46	207	69	2.87	73	Triam (9 puffs)
17	M	25	204	68	2.35	54	Theo (600 mg)
18	M	39	164	66	2.70	71	—
19	M	18	183	73	3.68	73	—
20	F	44	142	65	2.31	78	—
21	M	43	200	69	2.78	69	—
22	F	38	163	64	2.05	68	—
23‡	F	36	151	62	2.14	73	—
24‡	M	29	185	69	2.45	56	Beclo (2 puffs)
25	M	36	194	70	2.27	52	Beclo (16 puffs)
26	M	20	145	67	2.94	67	—
27	M	41	231	72	3.05	68	—
28	M	18	236	74	3.42	70	—
29	F	51	125	58	1.53	71	Beclo (8 puffs) Theo (600 mg)
Median		34	175	69	2.48	68	
Range		18-54	125-236	58-75	1.53-3.68	49-80	

Triam, Inhaled triamcinolone; Beclo, inhaled beclomethasone; Theo, oral theophylline.

*Obtained at the prestudy visit.

†Excludes inhaled β -agonist agents, which were taken by all patients; formulations of inhaled corticosteroids. Approved for use in the United States.

‡Denotes patients discontinued during the study: no. 9, during period I - personal issues; no. 12: period II - asthma attack; no. 23: period II - rash; no. 24: after period I, before period II - upper respiratory tract infection.

symptoms, nocturnal awakenings, and as-needed β -agonist use). On study day 11 (last dose), baseline and postdosing spirometry were performed as they were for the first dose, with the exception of an additional set of measurements 12 hours after this final dose. If a patient's FEV₁ fell by more than 40% or if bothersome clinical symptoms developed during observed dosing, inhaled albuterol therapy was administered.

Study medication

Montelukast (50 mg) hard gelatin capsules and identical-appearing placebo capsules were supplied by

Merck Research Laboratories (Rahway, N.J.). Thus each study dose consisted of four capsules.

Spirometry measurements

The greatest FEV₁ value from a set of at least three acceptable, reproducible maneuvers (according to American Thoracic Society criteria) was considered the true value. Before initiation of the study, spirometry technicians demonstrated the ability to coach patients in the performance of spirometry according to American Thoracic Society standards; technician standards were reviewed consistently throughout the study.

Patient diary cards

All patients received diary cards, previously shown to have acceptable measurement properties as an evaluative instrument,¹³ during the baseline and treatment periods. The diary had two parts: daytime and nocturnal. Patients completed the daytime part (four daytime asthma symptom questions, rated on a scale of 0 to 6; Appendix) each evening at bedtime to assess daytime asthma symptoms since awakening and the nocturnal part (nocturnal awakenings on a 4-point scale, Appendix) on waking each morning before taking any medication. Diary cards were also used to record as-needed β -agonist use.

Tolerability evaluation

Tolerability of study treatment was evaluated by patient-reported adverse events and clinical assessment of laboratory (obtained after approximately every seventh dose) and physical examination data.

Statistical considerations

Analysis. In each treatment period, the mean of the FEV₁ values measured 30 and 15 minutes before the first dose was considered the baseline value. The FEV₁ percent change from the predose baseline was measured 3 and 4 hours after the first dose and 3, 4, and 12 hours after the thirty-first dose. Daytime asthma symptom and nocturnal awakening scores and as-needed β -agonist use were determined during the 2-week, open, prerandomization period as the mean daily value. During each treatment period, a mean daily score was determined.

For each variable, the difference between treatment periods was determined by a standard analysis of variance (ANOVA) model for a two-period crossover study including sequence, patient within sequence, period, treatment, and steroid by treatment interaction as factors. Missing data were not imputed. Special ANOVA techniques were not used to handle missing data; patients who discontinued treatment during period I (no period II data) were excluded from the ANOVA analyses but were included in the summary statistics. Variance for the difference in means (confidence intervals [CIs]) was determined from this ANOVA model. Normality and homogeneity of variance assumptions were tested with the Shapiro-Wilk and Levene's statistics, respectively. Comparisons between treatments were performed at a significance level of 0.05; no adjustment for multiplicity (end points and individual FEV₁ time points) was made because of the exploratory nature of the study.

Power. With a sample size of 15 for each subgroup (with and without inhaled corticosteroids), the study was designed to have 80% power to detect (at $\alpha = 0.05$, two-tailed test) a mean difference of 0.34 L between treatments in FEV₁ values at an individual specified time point (3 and 4 hours on day 1 and 3, 4, and 12 hours on day 11). In the combined group with a sample size of 28, the study had 80% power to detect (at $\alpha = 0.05$,

TABLE II. Baseline* FEV₁ values

Variable	No. of Patients	FEV ₁ (L)†
Period		
I	29	2.60 $\pm$ 0.71
II	27	2.75 $\pm$ 0.76
Treatment		
Montelukast alone	28	2.61 $\pm$ 0.75
Placebo alone	28	2.75 $\pm$ 0.72
Montelukast with inhaled corticosteroids	14	2.55 $\pm$ 0.87
Placebo with inhaled corticosteroids	13	2.72 $\pm$ 0.74
Montelukast without inhaled corticosteroids	14	2.67 $\pm$ 0.63
Placebo without inhaled corticosteroids	15	2.77 $\pm$ 0.74

*Predose one baseline; average of measurements made 30 and 15 minutes before dosing.

†Mean $\pm$ SD.

two-tailed test) a mean difference of 0.23 L in FEV₁ values at an individual specified time point.

RESULTS

Patient profile

Twenty-nine asthmatic (23 male and 6 female) patients were enrolled in the trial (Table I). Twenty-eight patients completed the first treatment period (one patient discontinued for personal reasons soon after the start of the period). Twenty-seven patients entered (one patient discontinued between treatment periods because of an upper respiratory tract infection) and 25 completed the second treatment period (two patients discontinued during the second treatment period because of a rash and an asthma exacerbation, respectively). Thus the ANOVA analysis included the 27 patients who entered period II; summary statistics included all available data from the original 29 patients.

Efficacy end points

No important deviations from the assumptions of the ANOVA model were found. Neither treatment, period effects, nor important quantitative differences (observed only at one FEV₁ measurement, day 11, hour 12) between treatment groups receiving and not receiving inhaled corticosteroids were observed.

The mean baseline FEV₁ values were comparable for treatment periods (periods I and II), treatment groups (montelukast and placebo), and be-

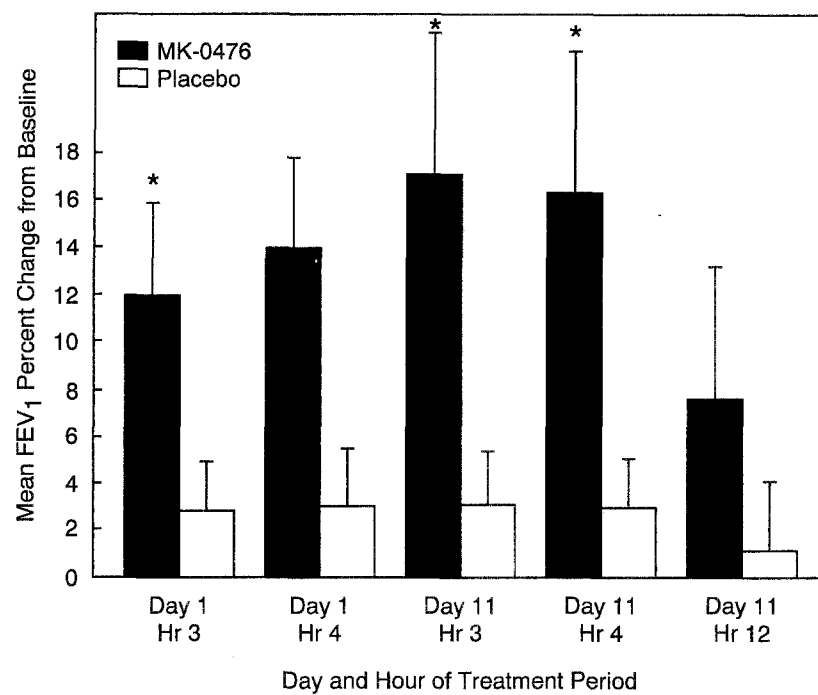


FIG. 1. Increase in FEV₁ (mean ± SEM on days 1 and 11 of each treatment period) as a percentage improved from the period-specific, day 1 predosing baseline value.

TABLE III. Change in patient reported end points

	Baseline*	Difference drug-placebo	95% CI for the difference
β-Agonist use (puffs/day)	5.38 ± 3.05	-1.0	(-1.61, -0.26)
Daytime symptom score†	2.61 ± 0.76	-0.35	(-0.64, -0.12)
Nocturnal symptom score‡	0.73 ± 0.53	-0.14	(-0.27, 0.00)

*Mean ± SD.

†0-6 score; composite of four questions.

‡0-3 scale.

tween patients receiving and not receiving inhaled corticosteroids (Table II).

Compared with placebo, montelukast improved FEV₁ on days 1 and 11 of treatments. The mean differences from placebo (percentage point differences for the percent change from baseline and 95% CIs) were 9.0% (95% CI 0.53, 18.72), 10.9% (95% CI -0.25, 20.20), 14.0% (95% CI 0.76, 31.43), 13.6% (95% CI 1.24, 28.83), 6.4% (95% CI -5.44, 25.20) for day 1, hours 3 and 4, and day 11, hours 3, 4, and 12, respectively. (Fig. 1).

Compared with placebo, decreases in daytime asthma symptoms and β-agonist use were observed with montelukast treatment; nocturnal asthma

scores also favored montelukast treatment (Table III).

Tolerability

A total of 11 patients reported 20 clinical adverse effects while receiving montelukast, and a total of 14 patients reported 23 clinical adverse effects while receiving placebo; additionally, the profile of adverse events reported was similar between treatment periods. During montelukast treatment, two patients were discontinued from the trial because of adverse events: one patient had a mild upper respiratory tract infection between treatment periods and one patient had a maculo-

popular rash while receiving concomitant ciprofloxacin therapy. None of the adverse events reported by the center investigator in patients receiving montelukast were serious or considered to be causally related to drug treatment. With placebo treatment, one patient required hospitalization because of worsening asthma on day 11 and was discontinued from the study.

Among the 28 patients enrolled, two laboratory adverse events were reported during montelukast treatment. One patient experienced a mild, transient rise in total bilirubin before the dose 7 measurement (pretreatment value, 0.4 mg/dl increasing to 1.3 mg/dl [upper limits of normal, 1.2 mg/dl] and returning to 0.5 mg/dl before dose 13). The second patient experienced a mild, transient rise in serum alanine aminotransferase before the twenty-second dose measurement (predose 13 value, 21 IU/L increasing to 41 IU/L [upper limit of normal, 31 IU/L] at the end of treatment and returning to 30 IU/L at the completion of the study).

DISCUSSION

This first multiple-dose trial of montelukast (200 mg three times daily for 10 1/3 days) in patients with chronic asthma demonstrates that this orally active, potent, and selective cysteinyl LT₁ receptor antagonist improves objective and subjective measurements of asthma; compared with placebo, significant improvements in FEV₁ and daytime asthma symptoms/activity scores and a decrease in as-needed β -agonist use were observed. The improvement in the nocturnal awakening score, which favored montelukast treatment, approached statistical significance.

This study also demonstrated that the clinical benefits observed in patients receiving montelukast occurred irrespective of the presence of concomitant inhaled corticosteroids. Previous *in vitro* work suggested that corticosteroids inhibited the production of arachidonic acid and its metabolites, the precursors of LTs, from isolated human inflammatory cells.¹⁴ However, more recent *in vivo* studies suggest that the cysteinyl LTs are released into the airways of patients with asthma, despite treatment with high doses of oral corticosteroids.¹⁵ Thus it may be hypothesized that agents that affect the action of LTs may complement corticosteroid therapy in the treatment of asthma.

The significant clinical improvements noted in this study suggest that montelukast may have a role in the treatment of patients with chronic asthma. Although clinical crossover designs often have

confounding factors, in this trial neither treatment nor period effects were noted. Clearly, parallel-group clinical trials of longer duration are needed to fully assess the clinical effects of montelukast in patients with asthma.

How the cysteinyl LTs affect the human airway is not completely understood. However, the clinical improvements noted in patients receiving multiple-dose montelukast provide important evidence for the role of these LTs as mediators of asthma symptoms. In clinical trials of other LT inhibitors, similar improvement in the end points of pulmonary function and decreases in asthma symptoms and as-needed β -agonist use have been noted.^{16,17} In a double-blind, randomized, placebo-controlled, dose-ranging study, treatment with 20 mg of ICI 204,219 twice daily for 6 weeks resulted in significant improvements in asthma end points compared with placebo.¹⁶ Patients receiving the 20 mg twice daily dose reported a significant reduction in nighttime awakenings, daytime asthma symptoms, and albuterol use and improvements in FEV₁. In a randomized, double-blind, placebo-controlled trial of zileuton (a 5-lipoxygenase inhibitor), patients receiving the 2.4 gm/day dose experienced significant improvements in airway function and decreases in asthma symptoms and β -agonist use after 4 weeks of therapy.¹⁷

In this first multiple-dose trial, montelukast, 600 mg/day, administered over an extended period of time (i.e., 10 1/3 days) was generally well tolerated. Adverse events were reported with similar frequency in the montelukast and placebo treatment periods.

This trial demonstrates that montelukast, a CysLT₁ receptor antagonist, at a dose of 600 mg/day, provides benefit in the treatment of chronic asthma. Clinical trials of longer duration with a parallel-group design, lower total daily doses, and less frequent dosing intervals are needed to investigate the long-term, clinical benefit of montelukast.

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APPENDIX

Daytime symptom score

1. How *often* did you experience asthma symptoms?

None of the time	All of the time
0	6
2. How much did your asthma symptoms *bother* you?

Not at all bothered	Severely bothered
0	6
3. How much activity could you do today?

More than usual activity	Less than usual activity
0	6
4. How often did your asthma affect your activities?

None of the time	All of the time
0	6

Nighttime asthma

1. Did you wake up with asthma?
 No _____ Yes _____
2. How often? (Select the appropriate number)
 1 = once
 2 = more than once
 3 = awake "all night"