Montelukast, a Once-Daily Leukotriene Receptor Antagonist, in the Treatment of Chronic Asthma

A Multicenter, Randomized, Double-blind Trial

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Objectives: To determine the clinical effect of oral montelukast sodium, a leukotriene receptor antagonist, in asthmatic patients aged 15 years or more.

Design: Randomized, multicenter, double-blind, placebo-controlled, parallel-group study. A 2-week, single-blind, placebo run-in period was followed by a 12-week, double-blind treatment period (montelukast sodium, 10 mg, or matching placebo, once daily at bedtime) and a 3-week, double-blind, washout period.

Setting/Patients: Fifty clinical centers randomly allocated 681 patients with chronic, stable asthma to receive placebo or montelukast after demonstrating a forced expiratory volume in 1 second 50% to 85% of the predicted value, at least a 15% improvement in forced expiratory volume in 1 second (absolute value) after inhaled β-agonist administration, a minimal predefined level of daytime asthma symptoms, and inhaled β-agonist use. Twenty-three percent of the patients used concomitant inhaled corticosteroids.

Primary End Points: Forced expiratory volume in 1 second and daytime asthma symptoms.

Results: Montelukast improved airway obstruction (forced expiratory volume in 1 second, morning and evening peak expiratory flow rate) and patient-reported end points (daytime asthma symptoms, “as-needed” β-agonist use, nocturnal awakenings) (P<.001 compared with placebo). Montelukast provided near-maximal effect in these end points within the first day of treatment. Tolerance and rebound worsening of asthma did not occur. Montelukast improved outcome end points, including asthma exacerbations, asthma control days (P<.001 compared with placebo), and decreased peripheral blood eosinophil counts (P<.001 compared with placebo). The incidence of adverse events and discontinuations from therapy were similar in the montelukast and placebo groups.

Conclusions: Montelukast, compared with placebo, significantly improved asthma control during a 12-week treatment period. Montelukast was generally well tolerated, with an adverse event profile comparable with that of placebo.

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ASTHMA IS a significant worldwide health problem, accounting for $4.2 billion of health care costs in the United States in 1995. Despite the development and institution of treatment guidelines, asthma remains a costly clinical problem, with a continuous need for new, innovative treatments. Current therapies have limitations, including poor compliance (inhalers, dosage frequency) and side effects. New, effective, well-tolerated oral therapies may have a substantial impact on the management of asthma.

The role of the cysteinyl leukotrienes (leukotrienes C4, D4, and E4) in asthma has been clearly established. These leukotrienes are produced and released from proinflammatory cells, including eosinophils and mast cells, and are at least 1000 times more potent bronchoconstrictors than histamine or methacholine in normal and asthmatic subjects. The leukotrienes mediate many of the pathophysiological processes associated with asthma, including microvascular leakage, bronchoconstriction, and eosinophil recruitment into the airways. Agents that interrupt the action of the leukotrienes (5-lipoxygenase inhibitors and leukotriene receptor antagonists) have demonstrated improvement of chronic asthma in clinical trials, thus providing evidence for their role in asthma.

Montelukast sodium is a potent and specific leukotriene receptor antagonist that has been shown to have substantial blockade of airway leukotriene receptors 24 hours after oral dosing. This long du-
PATIENTS AND METHODS

STUDY DESIGN

This multicenter, randomized, double-blind, placebo-controlled, 3-period, parallel-group trial compared the clinical effect of oral montelukast sodium, 10 mg once daily at bedtime, and placebo. The study consisted of a 2-week, single-blind, placebo run-in period (period 1); a 12-week, double-blind, active treatment period (period 2); and a 3-week, double-blind, placebo washout period (period 3). Clinic visits occurred every 2 weeks during period 1 and every 3 weeks thereafter.

The study was conducted at 50 study centers in the United States between October 21, 1994, and August 13, 1995; 681 patients were randomly assigned, according to a computer-generated allocation schedule, to receive either a film-coated tablet of montelukast sodium, 10 mg, or matching placebo. In period 3, a subset of patients was blindly switched from montelukast to placebo according to the computer-generated allocation schedule.

Written informed consent approved by the respective institutional review boards was obtained from each patient. If the patient was younger than 18 years, consent was also obtained from the patient’s parent or guardian.

INCLUSION CRITERIA

Healthy, nonsmoking patients (male and female), aged 15 years and older with at least 1 year of intermittent or persistent asthma symptoms, were enrolled. Female patients had a negative serum β-human chorionic gonadotropin test at the prestudy visit. All patients used short-acting inhaled β-agonists as needed to treat their asthma, and a percentage of patients (not to exceed 25%) were allowed concomitant inhaled corticosteroids at a constant dosage beginning at least 4 weeks before the prestudy visit. Patients with non–life-threatening, clinically stable, concomitant diseases could be enrolled in the study.

Patients were eligible for randomization if they had, at least 2 of the 3 visits during period 1, a forced expiratory flow in 1 second (FEV₁) between 50% and 85% of the predicted value (after withholding β-agonist for at least 6 hours) and an absolute increase in FEV₁ of at least 15%. Patients were required to have a minimum total 2-week daytime asthma symptom score of 64 (a maximum score of 336 was possible) and to have used a daily average of at least 1 puff of β-agonist during period 1.

Patients received a peak flow meter (Mini-Wright; Clement Clark, Columbus, Ohio) and a practice diary card at the prestudy visit. Patients who demonstrated competence with the use of these instruments and the ability to perform reproducible spirometry at each clinic visit were eligible for period 2.

EXCLUSION CRITERIA

Active upper respiratory tract infection within 3 weeks, acute sinus disease requiring antibiotic treatment within 1 week, emergency department treatment for asthma within 1 month, or hospitalization for asthma within 3 months before the prestudy visit were study exclusions. Excluded medications included oral, inhaled (concomitant inhaled medication use was allowed for a subset of patients), and parenteral corticosteroids within 1 month; cromolyn sodium, nedocromil sodium, theophylline, and loratadine within 2 weeks; theophylline (oral and intravenous), β-agonists (oral or long-acting inhaled), and anticholinergic agents within 1 week; astemizole within 3 months; and immunotherapy initiated within 6 months before the prestudy visit. According to a standardized protocol, oral corticosteroids were allowed for treatment of worsening asthma during periods 2 and 3. Patients who required rescue during period 1, more than 2 rescues during periods 2 and 3, or change in immunotherapy were discontinued from the study.

EVALUATIONS

The FEV₁, and daytime asthma symptom score were pre-specified as primary end points. Other prespecified end points were morning and evening peak expiratory flow rate (PEFR), daily use of inhaled short-acting as-needed β-agonist, nights per week with nocturnal awakenings, asthma-specific quality of life, physician’s and patient’s global evaluations, change in peripheral blood eosinophil counts, and asthma outcome end points including episodes of worsening asthma (percentage of days with asthma exacerbations), use of rescue oral corticosteroids (percentage of patients), discontinuation because of worsening asthma (determined by whether additional asthma medications were required), and asthma control days.

Spirometry was performed at each clinic visit between 6 and 9 AM, approximately 10 to 12 hours after the previous dose of study medication and after β-agonist and short-acting antihistamines had been withheld for at least 6 and 48 hours, respectively. Patients using inhaled corticosteroids were instructed to take the morning dose either an hour before or after a clinic visit. The spirometry measurements were collected with a standard spirometer (Nellcor/Puritan-Bennett PB 100/PB 110, Lendena, Kan) and transmitted via modem to a central spirometry quality control center, where the data were reviewed to ensure uniform adherence to American Thoracic Society standards of acceptability and reproducibility.¹³ Continual per-
formance feedback was given to clinical centers to maintain and enhance spirometry quality. The largest FEV₁ from a set of at least 3 maneuvers was the visit value. Airway reversibility was evaluated at each visit during period 1 and at predefined visits during periods 2 and 3.

The daily diary card contained daytime asthma symptoms and nighttime awakening scales, previously shown to have acceptable evaluative measurement properties. The 4 daytime asthma symptom questions addressing the severity and bothersomeness of asthma symptoms (using a 7-point scale where 0 indicates best and 6, worst) were combined into a mean daily score. Nighttime awakenings were evaluated by the response to a single question by means of a 4-point scale ("no awakenings" to "awake all night"). The change in nocturnal awakenings was determined for the prespecified group of patients with 2 or more nights with awakenings per week during the run-in period.

The PEFR was measured by the patient in the morning, on arising, and in the evening, at bedtime, before taking the study medication. The largest of 3 measurements was recorded on the diary card, and measurements performed within 4 hours of β₂-agonist use were identified. The patients also recorded as-needed β₂-agonist use during the day and at night, and oral corticosteroid rescue, visit to a physician's office, or hospitalization because of worsening asthma. At the completion of period 2 (week 12), physicians and patients independently evaluated the change in the patient's asthma (global evaluations) by selecting the most appropriate response by means of a 7-point scale ("very much better," "moderately better," "a little better," "unchanged," "a little worse," "moderately worse," "very much worse"). At the randomization visit (before patients received study medication) and at the end of period 2 (week 12), the patients also completed the validated Asthma Quality of Life Questionnaire. The questionnaire contained 32 questions divided into 4 quality-of-life domains—activity, symptoms, emotions, and environment—with responses on a 7-point scale where 0 indicates worst and 6, best.

An asthma exacerbation day was defined as a day when any 1 of the following occurred: a decrease of more than 20% from baseline in morning PEFR, PEFR less than 180 L/min, an increase of more than 10% from baseline in β₂-agonist use (a minimum increase of 2 puffs), an increase of more than 30% from baseline in symptom score, "awake all night" with asthma, or worsening asthma requiring oral corticosteroid rescue, visit to a physician's office, or hospitalization. An asthma control day was defined as any day when none of the following occurred: worsening asthma requiring oral corticosteroid rescue, visit to a physician's office or hospitalization, nocturnal awakenings, or use of more than 2 puffs of β₂-agonist.

Blood samples were obtained before and 3, 6, 12, and 15 weeks after randomization to period 2. Clinical laboratory tests (ie, hematology, serum chemistry, and urinalysis) and blood eosinophil counts (determined by an automated cell counter in a central laboratory) were performed. Female patients had serum β-human chorionic gonadotropin measured at the prestudy visit and either a serum or urine pregnancy test at each visit. A complete physical examination and 12-lead electrocardiogram were performed before and after randomization; vital signs were recorded at each visit.

### Statistical Methods

The primary analysis was an intention-to-treat approach including all randomized patients with a baseline value and at least 1 treatment period measurement. The data were analyzed as averages during the treatment period, and data points were not carried forward. For end points analyzed as change or percentage change from baseline, the average period 1 measurement was the baseline value. The mean period 2 response was compared between treatment groups by means of an analysis of variance (ANOVA) model that included terms for treatment, inhaled corticosteroid use (stratum), and study center. The between-group differences of within-group change and the 95% confidence interval (CI) were computed on the basis of the ANOVA model. Quality of life and the global evaluations were analyzed by the ANOVA model. In addition, the 7 categories of the global evaluations were collapsed into 3 categories (better, no change, and worse) and analyzed with a Cochran-Mantel-Haenszel test to corroborate the ANOVA results.

Assumptions of normality and homoscedasticity were assessed. All statistical tests were 2 tailed, and P ≤ .05 was considered statistically significant.

The safety evaluations included all randomized patients. The number and percentage of patients reporting clinical adverse experiences and laboratory abnormalities were summarized by treatment group.

### Power and Sample Size

The study was designed with a sample size of 300 and 200 patients for montelukast and placebo groups, respectively, to have 95% power to detect (α = .05, 2-tailed test) a mean difference between treatment groups of 5.4 percentage points in FEV₁ (percentage change from baseline) and 9.1% in daytime symptom score (change from baseline).

### Efficacy

Montelukast significantly improved (P < .001 compared with placebo) airway obstruction, as shown by an increase in FEV₁ of 13.1% (placebo, 4.2%), in morning PEFR of 24.0 L/min (placebo, 4.6 L/min), and in evening PEFR of 15.9 L/min (placebo, 4.2 L/min). The mean difference compared with placebo, based on ANOVA, was 8.9% (95% CI, 6.8% to 11.0%) for FEV₁, 19.4 L/min (95% CI, 14.2 to 24.5 L/min) for morning PEFR, and 11.6 L/min...
Week treatment period (telukast (95% CI, 6.9 to 16.3 L/min) for evening PEFR. The improvement observed in evening PEFR indicated that montelukast provided protection throughout the 24-hour dosing interval. Also, patient-reported end points, eg, daytime asthma symptoms and as-needed ß-agonist, were significantly (P<.001 compared with placebo) improved by montelukast (Figure 2). Furthermore, patients reported significantly less nocturnal awakening (−1.66 and −0.80 nights per week for montelukast and placebo, respectively); the mean difference, based on ANOVA, was −0.87 (95% CI, −1.22 to −0.53).

The improvements observed in airway obstruction and patient-reported end points were maintained consistently throughout the 12-week treatment period 2 (Figure 2). The prespecified patient subgroup that was blindly switched from montelukast to placebo during period 3 showed the treatment effects returned toward, but not past, the placebo group, confirming the beneficial effects of montelukast, and withdrawal of montelukast did not cause rebound worsening of asthma (Figure 2).

Within 1 day of dosing, montelukast achieved near-maximal effect as shown by the response during the first 21 days of period 2. Figure 3 illustrates this rapid, beneficial response for ß-agonist use, daytime asthma symptoms, and morning PEFR. Similar improvements were seen in nocturnal awakenings and evening PEFR. In addition, each asthma-specific quality-of-life domain had significantly higher scores for patients treated with montelukast (P<.001 compared with placebo) during the 12-week treatment period (Figure 4). Also, patients’ and physicians’ global evaluations demonstrated that patients receiving montelukast had significantly improved asthma control compared with patients receiving placebo (Figure 5). Patients treated with montelukast experienced fewer days with asthma exacerbations (a decrease of 31%) and more asthma control days (an increase of 37%) than patients receiving placebo (P<.001) (Figure 6). Fewer patients (a decrease of 28%) treated with montelukast required oral corticosteroid rescues (6.9% compared with 9.6% for placebo; P=.20), and fewer patients (a decrease of 59.5%) discontinued therapy because of worsening asthma (1.5% compared with 3.7% for placebo; P=.07).

Montelukast significantly decreased peripheral blood eosinophil counts (P<.001 compared with placebo) (Figure 7).

There was no correlation between the improvements in FEV1 or daytime asthma symptom scores and patients’ baseline values. Furthermore, there were no clin-
cally significant interactions between the prespecified subgroups of age, sex, race, history of allergic rhinitis, history of exercise-induced asthma, study center, and concomitant use of inhaled corticosteroid and these study end points. For example, patients taking concomitant inhaled corticosteroids had an increase in FEV1 of 10.3% with montelukast (1.6% with placebo), and patients without corticosteroids had an increase in FEV1 of 13.9% with montelukast (5.0% with placebo).

SAFETY

The overall frequency of clinical adverse events reported by patients was similar between the montelukast and placebo groups. Upper respiratory tract infection and headache were the most frequently reported clinical adverse events, similar in incidence between treatments (Table 3). Twelve patients (4.4%) in the placebo group and 9 (2.2%) in the montelukast group discontinued treatment because of adverse experiences. Six of the 12 patients in the placebo group discontinued because of asthma, 2 because of bronchitis, and the other 4 because of depression, facial edema, endometriosis, and headache. Three of the 9 montelukast-treated patients discontinued treatment because of asthma; the other 6 patients discontinued because of anxiety, depression, dyspnea, gastritis, back pain, and respiratory failure.

There was no difference in the frequency of laboratory adverse events between the montelukast (7.1%) and placebo (5.5%) groups. The most frequently reported event was increased levels of alanine aminotransferase: 2.5% with montelukast and 1.5% with placebo treatment. Serum alanine and aspartate aminotransferase elevations more than 2 times above the upper limit of normal were infrequent in both the montelukast and placebo groups (≤0.9% and ≤1.5%, respectively). Also rare (≤0.7%), elevations of alkaline phosphatase and serum bilirubin levels were similar in incidence between treatment groups. Laboratory abnormalities either returned toward normal while study therapy was continued, or had explanations not related to study medications, such as weight-lifting and minor blunt trauma injuries. No laboratory adverse event caused discontinuation.
This clinical trial demonstrates that montelukast provided clinical benefit during the 12-week treatment period by consistent and significant improvement of all asthma control variables compared with placebo. Montelukast improved airway obstruction, patient-reported end points, and asthma outcomes (protection against worsening asthma episodes), consistent with the goals of asthma therapy as outlined in the Global Initiative for Asthma. 

For each end point, the effect of montelukast was consistent throughout the double-blind treatment period (period 2), indicating that tolerance did not develop. Tolerance can be a clinical problem with some therapies, including receptor antagonists. After 12 weeks of treatment, removal of montelukast did not cause rebound worsening of asthma in any end point. Rebound worsening on treatment discontinuation has been experienced with re-
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ceptor antagonists,17 possibly because of target cell recep-
tor up-regulation.18 Since receptor up-regulation is thought
to occur within the first week of exposure,19 it is unlikely
that rebound worsening of asthma will occur.

Studies with zafirlukast, another leukotriene recep-
tor antagonist, and zileuton, a 5-lipoxygenase inhibitor,
have demonstrated that these compounds also provide ben-
efits in chronic asthma. Zafirlukast improved airway ob-
struction in a 6-week study,6 and zileuton improved air-
way obstruction and patient-reported end points in a 12-
week study.20 These trials showed large variability in the
treatment effects across end points,6,7,20 in contrast to the
consistent effect shown with montelukast in this trial.

In this study, all end points were measured with high
precision, leading to accurate and consistent treatment ef-
fest estimates. Spirometry data, transmitted via mod-
em, were collected and assessed centrally, with timely
feedback given to study centers. We believe that the stan-
dardized, centralized spirometry quality control insti-
tuted in this study was the reason not only for the accu-
ricy of the spirometry measurements, but indirectly for
the precision of all study end points. Further evidence of
the benefit of centralized quality control was shown in
the decreased variability (the root mean square error
from the ANOVA model) of the data in this large clini-
cal trial compared with that of a smaller dose-ranging
study.9 To our knowledge this is the first report of the

use of an electronic, centralized spirometry control sys-
tem in a therapeutic asthma clinical trial.

The diary card measures (daytime asthma symp-
tom scores, nocturnal awakening, β-agonist use, and
PEFR) demonstrated a near-maximal effect of mon-
telukast within the first day of treatment, indicating a rapid
therapeutic benefit. Such a rapid onset has not been seen
with other leukotriene receptor antagonists or 5-
lipoxygenase inhibitors used in the treatment of
asthma.7,21,22 Other controller agents for asthma, includ-
ing cromolyn, nedocromil, and inhaled corticosteroids,
also require a longer treatment duration before their ef-
fects become apparent.7,24

Significant improvements in all quality-of-life domains
(symptoms, activity, environment, and emotions) occurred
with montelukast treatment. Previous work in this area25
suggests that the magnitude of the treatment-related im-
provements observed in this study were clinically mean-
ingful. The evaluation of quality of life is important because
it determines the impact of therapy on the patient’s daily
life that is not captured by other end points.14

Another important objective of chronic asthma
therapy is the protection against episodes of worsening
asthma.26 Such episodes have been shown to contribute to
morbidity and consume substantial asthma-related
health resources. We found that montelukast protected
significantly against asthma worsening. A 31% decrease
in asthma exacerbation days and a 37% increase in asthma
control days were observed. In addition, montelukast provided protection against episodes of worsening asthma (need for oral corticosteroid rescue treatment or discontinuation from study therapy). These results confirmed findings from a previous montelukast trial and were consistent with the improvements in the primary end points of this study.

The effect of montelukast was generally consistent across patient prerandomization characteristics, including demographic variables and baseline values for the end points (FEV₁ and daytime symptom score), indicating that there was a similar clinical response to montelukast across subgroups of the asthmatic population studied. Montelukast provided clinical benefit in patients using concomitant inhaled corticosteroids, thus confirming previous clinical trials with montelukast. It has been shown that oral corticosteroids do not inhibit the production of leukotrienes in the airways of asthmatic patients; this provides the biological basis for the additive effects of leukotriene receptor antagonists and corticosteroids. It is currently believed that asthma is a syndrome of airway inflammation, characterized in part by increased numbers of blood eosinophils, which, with other inflammatory cells, infiltrate the airways. Leukotrienes have been shown to enhance proliferation of bone marrow eosinophil and basophil precursors, to attract eosinophils into the lung, and to cause microvascular leakage. The decrease in blood eosinophil counts over time, consistent with previous montelukast studies and similar to that seen with inhaled corticosteroids, suggests that montelukast may have important effects on measures of asthmatic inflammation. A study with a 5-lipoxygenase inhibitor has shown similar results. These observations suggest that the therapeutic effect of anti-leukotriene compounds may, in part, be caused by effects on inflammatory measures.

In conclusion, montelukast sodium, given orally at 10 mg once daily at bedtime during a 12-week treatment period, provided significant clinical benefit to patients with chronic asthma. It was generally well tolerated, with an adverse event profile comparable with that of placebo.

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