Montelukast for Chronic Asthma in 6- to 14-Year-Old Children
A Randomized, Double-blind Trial

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Context.—Leukotrienes are important mediators of asthma by causing bronchoconstriction, mucus secretion, and increased vascular permeability. Studies using compounds that block leukotrienes have demonstrated improvement in asthma control in adults and adolescents, but children younger than 12 years, for whom asthma is the most common chronic disease, have not been studied.

Objective.—To determine the clinical effect of montelukast, a leukotriene receptor antagonist, in 6- to 14-year-old children with asthma.

Design.—Eight-week, multicenter, randomized, double-blind study.

Setting.—Forty-seven outpatient centers at private practices and academic medical centers in the United States and Canada.

Patients.—A total of 336 children with forced expiratory volume in 1 second (FEV₁) between 50% to 85% of the predicted value, at least 15% reversibility after inhaled β-agonist administration, a minimal predefined level of daytime asthma symptoms, and daily β-agonist use. Concomitant inhaled corticosteroids at a constant daily dose were used by 39% of patients receiving montelukast and 33% receiving placebo.

Intervention.—After a 2-week placebo run-in period, patients received either montelukast (5-mg chewable tablet) or matching-image placebo once daily at bedtime for 8 weeks.

Main Outcome Measure.—Morning FEV₁ percent change from baseline.

Results.—Mean morning FEV₁ increased from 1.85 L to 2.01 L in the montelukast group and from 1.85 L to 1.93 L in the placebo group. This represents an 8.23% (95% confidence interval [CI], 6.33% to 10.13%) increase from baseline in the montelukast group and a 3.58% (95% CI, 1.29% to 5.87%) increase from baseline in the placebo group (P<.001 for montelukast vs placebo).

Conclusion.—Montelukast improves morning FEV₁ in 6- to 14-year-old children with chronic asthma.

ASTHMA IS the most common chronic illness of childhood, affecting approximately 10% of children. In the United States alone, approximately 22.2 million ambulatory care visits per year are made by children for the treatment of asthma. Worldwide, the prevalence of childhood asthma and hospitalizations for it are increasing. Current therapies for the treatment of asthma in children have limitations (eg, requiring inhalations, multiple daily administrations, or plasma drug level monitoring). Accordingly, new therapies that are effective, well tolerated, and easily administered would be advantageous in the treatment of childhood asthma.

Leukotrienes are important mediators of asthma. Leukotrienes are produced and released from inflammatory cells, including eosinophils and mast cells. They cause bronchoconstriction, mucus secretion, and increased vascular permeability. Studies using compounds that block leukotrienes (receptor antagonists and 5-lipoxygenase inhibitors) have demonstrated improvement in asthma control in patients aged 12 years and older. We know of no studies that have addressed the effect of leukotriene blockers in children with asthma younger than 12 years.

Montelukast (MK-0476) is an orally administered, specific leukotriene receptor antagonist. In recent adult studies, montelukast (10 mg once daily at bedtime) demonstrated improvement in parameters of asthma control, including forced expiratory volume in 1 second (FEV₁), daytime and nighttime symptom scores, and as-needed β-agonist use. The purpose of this 8-week study was to determine the effect of montelukast (5-mg chewable tablet administered once daily at bedtime), compared with placebo, on parameters of asthma control, including measurements of airways obstruction, patient-reported end points, and asthma outcomes, as well as to determine the safety profile in 6- to 14-year-old patients with asthma.

METHODS

Study Design

This was a multicenter, double-blind, randomized, placebo-controlled, 2-period, parallel-group study comparing the clinical effect of oral montelukast (5-mg chewable tablet) with matching-image placebo once daily at bedtime in 6- to 14-year-old children with asthma. The study consisted of a 2-week, single-blind, placebo run-in period and an 8-week, double-blind, active treatment period (Figure 1).

The study was conducted at 46 study centers in the United States and 1 study center in Canada between August 1995 and April 1996. All patients, study sites, and the coordinating center (Merck Research Laboratories) were blinded to treatment allocation. Unblinding of the database occurred on June 25, 1996. Patients were randomly allocated according to a computer-generated schedule in blocks of 5 (3 montelukast, 2 placebo) to receive either montelukast or placebo. Since airway patency is circadian, bedtime dosing was selected to provide higher plasma levels of montelukast coinciding with the time of maximal airways narrowing in the early morning hours. All patients used short-acting, inhaled β-agonists as needed to treat their asthma. A percentage of patients (not to exceed 40%) were allowed concomitant inhaled corticosteroids at a
constant dose and dosing interval, beginning at least 4 weeks before the pre-study visit. Oral corticosteroid rescue was permitted for worsening asthma during the study according to a pre-defined rescue plan. Patients requiring more than 1 course of oral corticosteroids were discontinued from the study.

Written informed consent approved by the respective institutional review boards (in the United States) or ethical review committee (in Canada) was obtained from the parents or guardians of all patients. Additionally, informed assent approved by the respective institutional review boards and ethical review committee was obtained from each patient.

Inclusion Criteria

Male and female outpatients, aged 6 to 14 years with a history of intermittent or persistent asthma symptoms, were enrolled. Eligibility for randomization included FEV₁ between 50% to 85% of the predicted value and an increase in FEV₁ of 15% or greater 20 to 30 minutes after inhalation of β-agonist at least twice during the prestudy visit and placebo run-in period. Patients were also required to have a minimum biweekly daytime asthma symptom score of 21 (see description of diary card below) and to have used, on average, at least 1 puff of albuterol per day during the 2-week run-in period. At the prestudy visit, patients received a peak flowmeter (Mini-Wright model, Clement Clark, Columbus, Ohio) and a practice diary card. To become eligible for the active treatment period, patients were required to demonstrate adequate understanding of and competency with these instruments as well as the ability to perform reproducible spirometry.

Exclusion Criteria

Study exclusions included 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, prior intubation for asthma, or hospitalization for asthma within 3 months before the prestudy (screening) visit. Excluded medications included astemizole within 3 months; oral, inhaled (if not already using concomitantly), or parenteral corticosteroids within 1 month; cromolyn, nedocromil, β-agonists (oral or long-acting), antimuscarinics, cimetidine, metoclopramide, phenobarbital, phenytoin, terfenadine, loratadine, or anticholinergic agents within 2 weeks; and theophylline within 1 week before the prestudy visit. Patients receiving immunotherapy had to maintain therapy at a constant dosage during the study, and therapy had to have begun at least 6 months before the prestudy visit. The use of new or changing doses of concomitant asthma medications by a patient, other than short-acting, inhaled β-agonists, resulted in discontinuation.

Evaluations

The FEV₁ was the prespecified primary end point. Other prespecified end points were daytime asthma symptoms; AM and PM peak expiratory flow rates (PEFs); daily use of inhaled, short-acting, as-needed β-agonist; nocturnal awakenings; pediatric asthma–specific quality-of-life questionnaire; global evaluations (physician, parent, patient, and combined); change in peripheral blood eosinophil counts; school loss; and asthma outcome endpoints, including episodes of severe worsening asthma (percentage of days and percentage of patients with an asthma exacerbation), use of rescue oral corticosteroids (percentage of patients), discontinuations because of worsening asthma (determined by whether additional asthma medications were required), and asthma-control days. Clinic-measured PEF was analyzed as a post hoc end point.

Spirometry (FEV₁ and PEF) was performed at each clinic visit between 6 AM and 9 AM. Inhaled β-agonists and short-acting antihistamines were withheld for at least 6 to 12 hours, respectively, prior to spirometry. Patients receiving scheduled concomitant inhaled corticosteroids withheld their morning dose until completion of a clinic visit. The largest FEV₁ from a set of 3 acceptable maneuvers at each clinic visit was recorded as the true value.

Airway reversibility (evaluated by measuring FEV₁ 20 to 30 minutes after administration of 2 puffs of albuterol) was tested at 2 visits during the run-in period and 4 and 8 weeks after randomization. Spirometry measurements were collected with a standard spirometer (Puritan Bennett PB 100/PB110, Wilmington, Mass). Each clinic center transmitted the spirometry data electronically to the central spirometry quality control center where the data were reviewed to ensure uniform adherence to American Thoracic Society standards of acceptability and reproducibility.

A daily diary card (validated for use in 6- to 14-year-old patients) that contained daytime asthma symptom and nighttime awakening scales was used in the study.

The 3 daytime asthma symptom scales (regarding the frequency and bother of asthma symptoms and activity limitations due to asthma on a 6-point scale of 0 to 5, where 0 is best) were combined into a mean daily score. Nighttime awakenings were evaluated by the response to a single question. Diary card questions were read verbatim by care-givers to patients aged 6 to 8 years and their responses recorded; patients aged 9 to 14 years answered and recorded diary card questions under adult supervision. Daytime symptoms were recorded on the diary card in the evening at bedtime and nocturnal awakenings in the morning on arising. The change in nocturnal awakenings was determined for a prespecified group of patients with 2 or more nights with awakenings per week during the run-in period.

The PEF was measured by the patient in the morning upon arising (AM PEF) and in the evening at bedtime (PM PEF) before taking study medication. The largest of 3 measurements was recorded on the diary card. The PEF measurements performed within 4 hours of β-agonist use were identified on the diary card. The patients also recorded as-needed β-agonist use during the day and at night, the use of oral corticosteroid rescue, and an unscheduled visit to a doctor’s office or hospitalization due to worsening asthma. On completion of the double-blind treatment period, parents, physicians, and patients independently evaluated the change in the patient’s asthma (global evaluations) by selecting the most appropriate response using a 7-point scale (very much better [score of 0], moderately better, a little better, unchanged, a little worse, moderately worse, very much worse [score of 6]).
Inhaled corticosteroid, % of patients 33 39
Male, % of patients 62 67
Duration of asthma, median (range), y 7 (0.5-15) 7 (0.5-14)

Statistical Methods

The study was designed with a sample size of 240 patients (96 in the placebo group and 144 in the montelukast treatment group) to have 90% power (2-sided test at α = .05) to detect a 7.1-percentage-point difference in FEV1 percent change from baseline between the 2 treatment groups.

RESULTS

Patients

A total of 336 patients entered the double-blind, active treatment period; 201 were assigned to montelukast and 135 to placebo treatment (Figure 1). There were no clinically meaningful differences between the montelukast and placebo treatment groups in their baseline characteristics (Table 1). Discontinuations from the study were similarly distributed between the montelukast and placebo treatment groups (12 [6%] and 10 [7%], respectively). Seven patients withdrew consent; 2 (1%) in the montelukast group and 5 (3.7%) in the placebo group. One patient (0.7%) in the placebo group was discontinued because of a protocol deviation. Two patients were unavailable for follow-up: 1 patient (0.5%) in the montelukast group and 1 (0.7%) in the placebo group. Eleven patients discontinued from the study because of an adverse experience: 8 (4%) in the montelukast group and 3 (2%) in the placebo group. One patient (0.5%) in the montelukast group discontinued because of a laboratory adverse experience.

Nine patients (5 in the montelukast group and 4 in the placebo group) were excluded in the intention-to-treat analysis of the primary end point (FEV1) because of missing baseline or treatment data or significant deviations from good clinical practice standards.
Table 2.—Efficacy End Points With Baseline Measurements

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Montelukast</th>
<th>P Value</th>
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<tbody>
<tr>
<td>FEV1, L§</td>
<td>1.85 ± 0.53</td>
<td>1.85 ± 0.55</td>
<td></td>
</tr>
<tr>
<td>Total daily β-agonist use, puffs§</td>
<td>3.24 ± 2.02</td>
<td>3.34 ± 1.91</td>
<td></td>
</tr>
<tr>
<td>Daytime asthma symptom, score</td>
<td>1.26 ± 0.63</td>
<td>1.28 ± 0.58</td>
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<tr>
<td>Clinic-measured AM PEF, L/min</td>
<td>270.52 ± 83.51</td>
<td>264.19 ± 81.9</td>
<td></td>
</tr>
<tr>
<td>Activity domain</td>
<td>4.83 ± 1.08</td>
<td>4.70 ± 1.07</td>
<td></td>
</tr>
<tr>
<td>Emotions domain</td>
<td>5.67 ± 1.26</td>
<td>5.38 ± 1.24</td>
<td></td>
</tr>
<tr>
<td>School loss, % of days</td>
<td>2.28 ± 2.91</td>
<td>2.20 ± 6.01</td>
<td></td>
</tr>
<tr>
<td>Eosinophils, cells × 10^9%</td>
<td>0.47 ± 0.33</td>
<td>0.44 ± 0.31</td>
<td></td>
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</tbody>
</table>

*Values are mean ± SD.

Table 3.—Efficacy End Points Without Baseline Measurements

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Montelukast</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parent’s global evaluation score</td>
<td>1.69 ± 1.34</td>
<td>1.34 ± 1.21</td>
<td>.049</td>
</tr>
<tr>
<td>Physician’s global evaluation score</td>
<td>1.96 ± 1.22</td>
<td>1.68 ± 1.26</td>
<td>.06</td>
</tr>
<tr>
<td>Patient’s global evaluation score</td>
<td>1.72 ± 1.23</td>
<td>1.46 ± 1.15</td>
<td>.11</td>
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<tr>
<td>Combined global evaluation score†</td>
<td>1.78 ± 1.10</td>
<td>1.49 ± 1.01</td>
<td>.04</td>
</tr>
<tr>
<td>Episodes of worsening asthma (days with an asthma exacerbation, %)</td>
<td>25.67 ± 24.65</td>
<td>20.58 ± 22.58</td>
<td>.049</td>
</tr>
<tr>
<td>Patients with an asthma exacerbation, %</td>
<td>95.5%</td>
<td>84.8%</td>
<td>.002</td>
</tr>
<tr>
<td>Rescue oral corticosteroid use, % of patients</td>
<td>15.8%</td>
<td>12.1%</td>
<td>.41</td>
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<tr>
<td>Discontinuations due to worsening asthma, % of patients</td>
<td>2.3%</td>
<td>3.5%</td>
<td>.74</td>
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<tr>
<td>Asthma-control days, % of days</td>
<td>55.20 ± 31.80</td>
<td>56.86 ± 33.57</td>
<td>.53</td>
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</tbody>
</table>

*Values are mean ± SD unless indicated otherwise.
†Average of parent, physician, and patient global evaluations combined.
§Expressed as a proportion of patients and not based on mean values.

Efficacy

Montelukast, compared with placebo, caused significant (P<.001) improvement in the primary end point, FEV1, percent change from baseline. Averaged over the 8-week treatment period, the least squares mean±SD percent change from baseline in FEV1 was 3.58%±13.38% and 8.23%±13.52% for the placebo and montelukast groups, respectively. The least squares mean difference between the 2 treatment groups was 4.65% (95% Cl, 1.92%-7.38%). The analysis of the percent change from baseline in FEV1, with height as a covariate demonstrated similar results: least squares mean difference of 4.90% (95% Cl, 2.15%-7.64%). Furthermore, the effect of montelukast on FEV1 was consistent (no loss of effect) over the 8-week treatment period (Figure 2).

Secondary outcomes are summarized in Tables 2 and 3. Montelukast, compared with placebo, demonstrated significant improvement in percent change in total daily as-needed β-agonist use (P=.01), percentage of days (P=.049) and percentage of patients (P=.002) with asthma exacerbations, all domains (symptom [P=.007], activity [P<.001], and emotions [P=.002]) of a pediatric asthma–specific quality-of-life questionnaire, parental (P=.049) and combined (P=.04) global evaluations, and clinic-measured AM PEF (P=.03). Figure 3 demonstrates that montelukast, compared with placebo, caused a significant decrease (P=.02) in peripheral blood eosinophil levels over the 8-week active treatment period. Other secondary outcomes (daytime asthma symptoms, patient-reported AM and PM PEFs, physician’s global evaluation, patient’s global evaluation, nocturnal awakenings, discontinuations because of worsening asthma, rescue oral corticosteroid use, asthma-control days, and school loss) did not reach statistical significance; the study, however, was not powered to detect a difference between treatment groups in an end point other than FEV1.

The onset of action of montelukast was analyzed using predefined patient-reported diary card parameters, including daytime asthma symptom scores, total daily as-needed β-agonist use, and patient-reported AM PEF measurements. Montelukast had a rapid onset of action (within 1 day of dosing). Figure 4 depicts the time response profile over the first 21 days of therapy for total daily as-needed β-agonist use. The difference in average values after the first dose between the montelukast and placebo treatment groups was significant (P=.02). Similar results over the first 21 days of therapy were observed for patient-reported AM PEF (P=.03); the results with daytime asthma symptom scores were not statistically significant but numerically favored montelukast (P=.06).

Of note, the effects of montelukast on FEV1 and total daily as-needed β-agonist use were consistent (ie, the interactions were not significant) across sex (P=.77 and .88, respectively), ethnic groups (P=.23 and .78, respectively), Tanner stage (P=.32 and .06, respectively), history of allergic rhinitis (P=.11 and .19, respectively), history of exercise-induced asthma (P=.25, respectively), and concomitant inhaled corticosteroid use (P=.82 and .53, respectively). Importantly, the montelukast treatment effect in patients aged 6 to 11 years and 12 to 14 years was comparable (mean percent change in FEV1 of 7.7% and 9.8%, respectively).

Safety

The most common adverse experiences were headache, asthma, and upper respiratory tract infection (Table 4). Overall, there were no significant differences between the montelukast and pla-
Montelukast demonstrated a consistent effect across all subgroups (age, sex, race, Tanner stage, history of allergic rhinitis, history of exercise-induced bronchoconstriction, and concomitant inhaled corticosteroid use) and baseline FEV₁ similar to adult studies. These findings suggest that a broad range of patients with asthma benefit from montelukast treatment. The similarity of effect in corticosteroid- and noncorticosteroid-using patients suggests that the treatment effect of montelukast may be additive to that of inhaled corticosteroids. Furthermore, in a recent adult study, treatment with montelukast permitted significant tapering of inhaled corticosteroids compared with placebo.

Montelukast improved several other asthma control end points. Montelukast demonstrated a statistically significant change in the parental and combined global evaluations of response to study therapy over the active treatment period. Importantly, montelukast demonstrated a statistically significant improvement in the mean percentage of days with an asthma exacerbation (asthma-exacerbation days) as well as in the percentage of patients who experienced at least 1 asthma exacerbation.

The eosinophil is an asthma inflammatory effector cell that plays a critical role in the pathogenesis of asthma. This cell and its mediators are found in increased

ceto treatment groups in the frequency of any adverse experience, with the exception of allergic rhinitis, which occurred significantly (P<.01) more frequently in the placebo group than in the montelukast group.

Eleven patients were discontinued from the study because of an adverse experience: 8 (4%) in the montelukast group and 3 (2%) in the placebo group. Of the montelukast-treated patients, 5 patients were discontinued because of asthma, 1 patient was discontinued because of pneumonia, 1 because of dehydration, and 1 because of an upper respiratory tract infection. Of the 3 placebo-treated patients, 2 were discontinued because of asthma and 1 was discontinued because of urticaria.

Eleven patients (5.5%) in the montelukast group and 2 (1.5%) in the placebo group had laboratory values considered adverse experiences during treatment, the majority of which were transient and self-limited. Importantly, there were no significant differences between treatment groups in the frequency of patients with serum transaminase (alanine aminotransferase and aspartate aminotransferase) elevations. One montelukast-treated patient was discontinued because of peripheral eosinophilia, an abnormality that had also been present at prerandomization testing.

COMMENT

This study demonstrates the therapeutic benefit of montelukast, a leukotriene receptor antagonist, in 6- to 14-year-old patients with chronic asthma. Patients treated with either as-needed β-agonist alone or inhaled corticosteroids had significant improvement in their asthma control when they received montelukast, 5-mg chewable tablet once daily at bedtime. Though the magnitude of the changes observed appeared modest, they were consistent with those reported in other pediatric trials using currently available therapies. Montelukast, compared with placebo, demonstrated significant improvements in FEV₁ (primary end point), clinic-measured AM PEF, total daily as-needed β-agonist use, all domains of a pediatric asthma-specific quality-of-life questionnaire, parental and combined global evaluations, percentage of days and percentage of patients with asthma exacerbations, and peripheral blood eosinophil levels. Other outcomes (daytime asthma symptoms, patient-reported AM and PM PEFs, physician’s global evaluation, patient’s global evaluation, nocturnal awakenings, discontinuations because of worsening asthma, rescue oral corticosteroid use, asthma-control days, and school loss) did not reach statistical significance; the study, however, was not powered to detect a difference between treatment groups in an end point other than FEV₁.

The onset of action of montelukast was rapid; treatment effects occurred within 1 day after the first dose, as assessed by diary card parameters: total daily as-needed β-agonist use and patient-reported AM PEF. Other controller agents for asthma, including cromolyn and inhaled corticosteroids, appear to require a longer treatment duration before their effects become evident. With inhaled corticosteroids, a treatment period of approximately 1 week may be needed before pediatric patients with moderate asthma demonstrate improvement in lung function. With cromolyn sodium, a treatment effect generally may require 1 week to 3 weeks of therapy.

Montelukast not only demonstrated a rapid onset of action, but its treatment effects were maintained consistently over time. There was no evidence of tolerance in this or a prior adult study, suggesting that montelukast continues to be effective in the long-term treatment of asthma.

Figure 3.—The effect of montelukast (closed circles) compared with placebo (open squares) on mean peripheral blood eosinophil counts over the 8-week active treatment period. Vertical lines represent SEs.

Figure 4.—Onset of action of montelukast. The effect of montelukast (closed circles) and placebo (open squares) on as-needed β-agonist use (mean percent change from baseline) during the first 21 days in the active treatment period. Vertical lines represent SEs.
Daytime asthma symptoms reported at home using a diary card improved (although not statistically significantly); a larger than anticipated placebo response masked the treatment effect. However, the symptoms domain of the quality-of-life questionnaire was statistically significant, suggesting that montelukast does improve asthma symptoms in children.

The rate of clinical adverse experiences between the montelukast and placebo groups was similar. Laboratory adverse experiences were infrequent, mild, transient, and similar in frequency between the montelukast and placebo groups. Furthermore, the incidence of elevated serum transaminase levels was similar between the montelukast and placebo groups. Overall, montelukast was generally well tolerated over the 8-week treatment period in 6- to 14-year-old patients. Future studies will be needed to determine the long-term safety profile of montelukast. However, no mechanism-based toxic effects have been identified to date.

In summary, this study demonstrated that montelukast once daily is effective therapy in 6- to 14-year-old patients with asthma. Montelukast was well tolerated and demonstrated a safety profile generally similar to placebo. These results are consistent with and confirm the results seen in adult studies with montelukast. Overall, the results of this study suggest that montelukast would be a well-tolerated and effective therapeutic option to current asthma therapies in 6- to 14-year-old patients.