Montelukast Reduces Asthma Exacerbations in 2- to 5-Year-Old Children with Intermittent Asthma

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The PREVIA study was designed to investigate the role of montelukast, a leukotriene receptor antagonist, in the prevention of viral-induced asthma exacerbations in children aged 2 to 5 years with a history of intermittent asthma symptoms. The study was a 12-month multicenter, double-blind, parallel-group study of patients with asthma exacerbations associated with respiratory infections and minimal symptoms between episodes. Patients were randomized to receive oral montelukast 4 or 5 mg (depending on age) (n = 278) or placebo (n = 271) once per day for 12 months. Caregivers recorded children's symptoms, β-agonist use, and health care resource use in a diary card. Over 12 months of therapy, montelukast significantly reduced the rate of asthma exacerbations by 31.9% compared with placebo. The average rate of exacerbation episodes per patient was 1.60 episodes per year on montelukast compared with 2.34 episodes on placebo. Montelukast also delayed the median time to first exacerbation by approximately 2 months (p = 0.024), and the rate of inhaled corticosteroid courses (p = 0.027) compared with placebo. Montelukast effectively reduced asthma exacerbations in 2- to 5-year-old patients with intermittent asthma over 12 months of treatment and was generally well tolerated.

Keywords: controlled clinical trial; leukotriene receptor antagonist; pediatric

Asthma generally begins and has its greatest prevalence in children younger than 5 years old (1–3). This age group often presents with intermittent symptoms (i.e., long asymptomatic periods interrupted by episodes of asthma generally in association with the common cold). The episodic nature of this type of asthma may be due to greater variability of asthma in young children, underreporting of symptoms because of reliance on second-hand caregiver report, increased susceptibility of respiratory infections, or decreased effectiveness of current controller treatment in the younger age group.

Predicting an asthma exacerbation in children younger than 5 years old is difficult because objective measurements are not generally available and documenting the episodes relies on second-hand caregiver reports. Although daily symptoms are rare, asthma exacerbations are more common in preschool individuals with asthma compared with school children with asthma irrespective of concurrent controller treatment. Exacerbations exhibit no apparent correlation with prior changes in symptoms or β-agonist use. Without such predictors, clinicians and caregivers are unable to take acute preventive steps to prevent or prepare for an exacerbation. Effective, well tolerated preventive therapy would therefore appear to be the strategy of choice.

Recognition of the importance of inflammation underlying the pathology of asthma has led to the recommendation that controller therapy with inhaled corticosteroids be used in all patients with *persistent* asthma (4, 5). Although use of systemic corticosteroids may reduce the number of hospitalizations, viral-induced exacerbations have shown disappointing response to corticosteroid treatments, and therapy with maintenance doses of inhaled corticosteroids has not demonstrated any meaningful or consistent clinical benefit in viral-induced asthma (6–8). No preventive therapy has thus far proven worthwhile, and guidelines only recommend therapy with β-agonists on demand for intermittent asthma (5).

Viral infections, predominantly with rhinovirus, account for up to 85% of childhood asthma exacerbations, daily symptoms, and exacerbations in children (9) and adults (10) with asthma. Evidence suggests that leukotrienes play a key role in viral-induced respiratory illness. The leukotriene C_4 concentrations in nasopharyngeal secretions of young children with viral-induced wheeze was elevated compared with children who reacted only with upper airway symptoms (11) and can be detected up to 28 days after the onset of viral-induced respiratory illness (12), suggesting the need for long-term treatment. The leukotriene receptor antagonist, montelukast, has proven efficacy in the control of asthma exacerbations in adults (13), school children (14), and preschool children (15) with persistent asthma and in adults with aspirin-intolerant asthma (16). In addition, montelukast significantly reduced symptoms and exacerbations from respiratory syncytial virus postbronchiolitis in infants without asthma (17).

The purpose of this study was to investigate the effect of regular montelukast therapy on asthma exacerbations in young children 2 to 5 years old with a history of intermittent asthma associated with the common cold and minimal symptoms between episodes. Some of the results of these studies have been previously reported in the form of an abstract at the American Thoracic Society International Conference (Orlando, FL, 2004) (18) and at the European Respiratory Society Meeting (Glasgow, Scotland, 2004) (19).

METHODS

Study Design

This was a multicenter, double-blind, parallel-group randomized study comparing the clinical effect of once-daily oral montelukast with placebo on the number of asthma exacerbation episodes in 2- to 5-year-old children with intermittent asthma. The study was conducted at 68 sites in 23 countries. Written informed consent approved by the

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respective institutional review boards or ethical review committees was obtained from parents or legal guardians of each patient.

The study consisted of a 1-week screening period; a 2-week, single-blind, placebo run-in period; followed by a 48-week, double-blind active treatment period. After the run-in period, patients were randomly assigned to receive montelukast 4-mg chewable tablet (5-mg chewable tablet if they turned age 6) or image-matching placebo.

Patients

Patients were between the ages of 2 and 5 years with a clinical history of intermittent asthma symptoms resulting from an upper respiratory infection (common cold). The symptoms were intermittent in nature characterized by the absence of symptoms and β-agonist use in a typical week over 3 months before the first visit. RAST testing for dog dander, cat dander, cockroach, *Alternaria alternata,* dust mites, and serum IgE levels was performed in all patients.

Virologic Testing

Sampling for virologic testing was performed only at selected centers with facilities to perform the procedures. Nasal aspirate samples were taken whenever the parents reported signs or symptoms of a cold in their child. This design was chosen to maximize the chances of virus detection by encouraging early sampling, while recognizing that not all colds would be associated with exacerbations. All samples were sent to a single center for virus identification using modifications of published polymerase chain reaction protocols. Viruses and atypical bacteria detected were rhinoviruses, enteroviruses, respiratory syncytial virus, influenza (AH1, AH3, B), parainfluenza viruses (types 1, 2, and 3), human metapneumoviruses, adenoviruses, coronaviruses (OC43, 229E), *Mycoplasma pneumoniae*, and *Chlamydia pneumonia*.

Efficacy Endpoints

The primary efficacy endpoint was the number of asthma exacerbation episodes defined as any three consecutive days with daytime symptoms (average score of four daily daytime symptom questions of at least 1.0 on each day) and at least two treatments of β-agonist per day, or rescue use of oral/inhaled corticosteroids during 1 or more days, or a hospitalization because of asthma. The end of an episode was a day out of the hospital with no daytime symptoms (average score or four daily daytime symptom questions of 0.25 or less) and less than two treatments of β-agonist use, and no use of oral corticosteroids. The secondary efficacy endpoints were the number of treatment courses of oral and inhaled corticosteroids, duration of the exacerbation episodes, percentage of days without asthma, severity of the exacerbation episode, blood eosinophil counts, proportion of patients with an exacerbation episode, time to first exacerbation episode, and asthma-related resource utilization.

Statistical Analysis

The main efficacy analysis was based on the modified intention-to-treat principal; that is, all patients who had been treated for at least 1 day and who had filled out the diary card for at least 1 day were included. Rates of exacerbation episodes were analyzed by applying a Poisson regression model adjusted for overdispersion. Time to first exacerbation was presented using Kaplan-Meier curves and treatment groups were compared using log-rank test. The seasonality of having an asthma exacerbation episode was explored using a time to first exacerbation analysis using season as a time-dependent covariate. Duration of exacerbation episodes, percentage of days without asthma, severity of exacerbation episodes, and blood eosinophil counts were analyzed using analysis of variance models. The total severity of an exacerbation episode was analyzed using the sum of the severity scores over the exacerbation episode duration. (Additional detail for methods are provided in the online supplement.)

RESULTS

Patients

A total of 768 patients were screened for eligibility, and 549 patients entered the double-blind active treatment period; 278 received montelukast and 271 received placebo. Of these, 265 in the montelukast group and 257 in the placebo group were included in the intention-to-treat analysis (Figure 1). There were no clinically meaningful differences between treatment groups for baseline characteristics (Table 1). The majority of patients (85%) had asthma symptoms no more than twice per week during the month before entry into the study and $\sim$ 67% of patients had not used oral corticosteroids for 1 year before study entry (Table 1). Approximately 45% of patients used inhaled corticosteroids in the 6 months before study entry. The mild nature of asthma between exacerbations is illustrated in Figure 2, which shows total asthma symptoms score for 30 days before and after an exacerbation normalized to the day the exacerbation was reported.

Compliance with the treatment regimen as assessed by tablet count was similar between groups. The average percentage of days in which patients were fully compliant was 98.2% in the montelukast group and 97.9% in the placebo group.

Efficacy

Montelukast significantly ($p \leqslant 0.001$) reduced asthma exacerbation episodes, the primary efficacy endpoint of the 12-month study compared with placebo (Table 2). The average yearly asthma exacerbation episode rate was 1.60 for the montelukast group compared with 2.34 for the placebo group. The relative exacerbation rate for montelukast compared with placebo was 0.68 (95% confidence interval 0.56–0.83), a 31.9% reduction. Exacerbation episodes over the 12-month period for individual patients are depicted in Figure 3 for the montelukast and placebo treatment groups. The time to first exacerbation was longer for patients in the montelukast group (median = 206 days) compared with placebo (median = 147 days) ($p = 0.024$) (Figure 4). A sensitivity analysis modifying several aspects of the definition of an asthma attack did not alter the outcome (i.e., montelukast significantly reduced exacerbation episodes). The results were consistent across subgroups (Table 3) and geographic regions (data not shown). Montelukast significantly reduced the overall rate of corticosteroid use by 31.6% ($p = 0.024$) and the rate of inhaled corticosteroid use by 39.8% ($p = 0.027$) compared with placebo (Table 2). Oral corticosteroid use was similar between groups (Table 2).

The proportion of patients with asthma episodes (at least three consecutive days with symptoms and a least two treatments of β-agonist use) was significantly lower in the montelukast group (45%) compared with the placebo group (56%) ($p = 0.008$). Over the course of the year, only 5% of all patients were hospitalized for asthma: 4.2% in the montelukast group and 5.8% in the placebo group. The proportion of patients with at least one unscheduled visit to a physician for asthma was 37.0% in the montelukast and 42.4% in the placebo group.

For patients with at least one exacerbation, the average duration and severity of an exacerbation episode were similar for both treatment groups. The median average duration and severity of an exacerbation episode was similar in the two treatment groups. The percentage of days without asthma was 75.8% in the montelukast group and 72.7% in the placebo group. The least squares mean difference between groups was 3.48% (95% confidence interval, −0.13, 7.08) in favor of montelukast ($p = 0.059$).

Montelukast significantly reduced peripheral blood eosinophils by 4% compared with a 3.7% increase in the placebo group, a difference in medians of 7.7% ($p = 0.010$).

The proportion of patients who missed any time from daycare, playschool, or school, and the proportion of patients whose asthma affected their caregivers were similar in both treatment groups and did not show any trend over time.

The risk of having an exacerbation of asthma was significantly greater in the fall and significantly lower in the summer for both

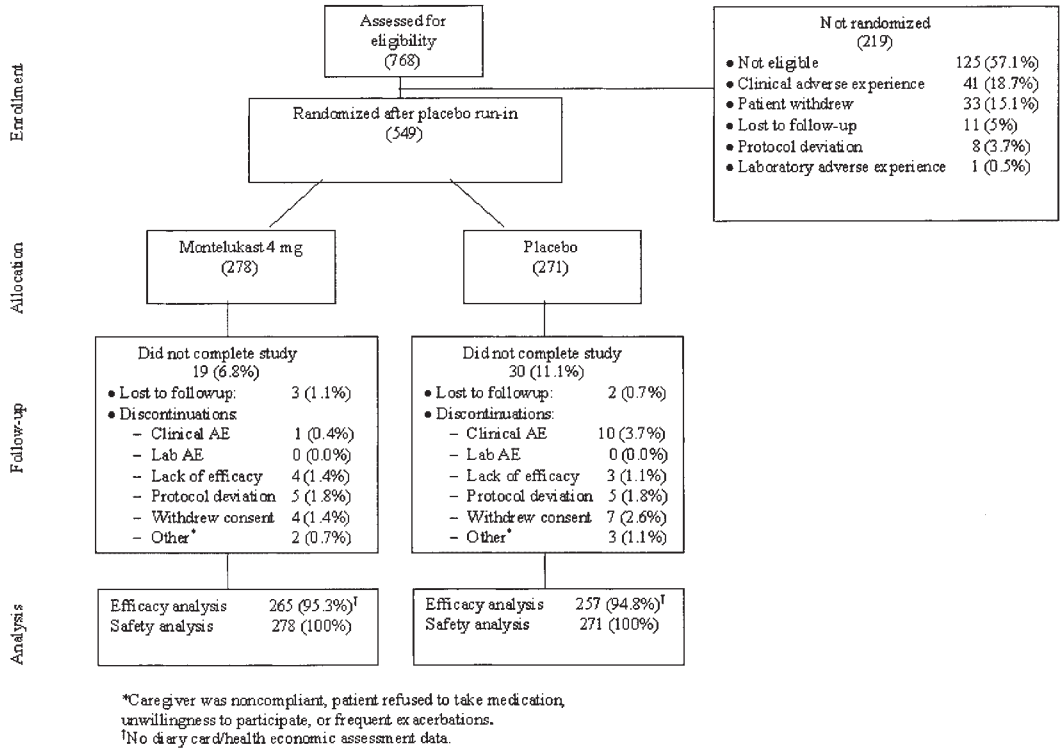

Figure 1. Study design.

treatment groups. Percentage of patients with an exacerbation episode is represented over the calendar year (normalized for hemisphere) for montelukast and placebo in Figure 5. The interaction between treatment and season effects was not significant ($p = 0.551$), indicating that the treatment effect was consistent throughout the year. When adjusted for season effect, montelukast significantly reduced the hazard of having an exacerbation episode compared with placebo ($p = 0.017$), corroborating the analysis of time to first exacerbation without season effect.

Virus Identification

Eight study centers selected for viral identification randomized 92 patients (46 montelukast, 46 placebo). Demographics of patients at these sites were similar to those of the total patient population (*see* Table E1 in the online supplement). A total of 158 nasal aspirates were taken; 65 in the montelukast group and 93 in the placebo group (patients may have had more than one aspirate). On average, 1.75 samples per patient per year were taken in the montelukast group and 2.46 in the placebo group, a reduction of 29% (95% confidence interval −3, 51) ($p = 0.070$), suggesting that caretakers perceived fewer incidents of cold symptoms in patients on montelukast.

Eighty-two samples (51.9%) were negative for all virology tests and 76 (48.1%) had at least one test positive. The most common positive tests were for rhinoviruses (27.6%), coronaviruses (9.0%), and respiratory syncytial virus (8.3%) (Table 4).

Fifty-two nasal aspirates were associated with an exacerbation. Virus was identified in 27 of these exacerbations. Because of this small number, treatment effect on exacerbations was not formally analyzed with respect to the presence of virus.

Safety

The proportion of drug-related adverse experiences was similar in both treatment groups occurring in 14 (5.0%) of patients in the montelukast group and 11 patients (4.1%) in the placebo group over the 12 months of treatment. There was one accidental overdose of montelukast that resulted in vomiting, after which the patient fully recovered. There were no serious laboratory adverse experiences and no laboratory adverse experiences leading to discontinuation of either therapy.

No patients in the montelukast group discontinued therapy because of an adverse experience considered by an investigator to be drug-related. Three patients in the placebo group discontinued therapy because of adverse experiences of abdominal pain, mood swings, or hypersensitivity considered to be drug-related. Three patients in the placebo group discontinued therapy because of asthma.

DISCUSSION

This study is the first to demonstrate beneficial controller therapy in 2- to 5-year-old patients with mild intermittent asthma. This study showed that once-daily treatment with montelukast significantly reduced asthma exacerbations related to respiratory tract infections compared with placebo over a 12-month period in 2- to 5-year-old patients with intermittent asthma. Montelukast also significantly reduced time to first exacerbation, as well as β-agonist and inhaled corticosteroid use. After an exacerbation occurred, the severity and duration of an exacerbation was similar in both treatment groups among patients. Montelukast was generally well tolerated; the incidence of drug-related adverse experiences was similar to placebo. The effect was independent of gender, age, race, atopic diathesis, allergy, or baseline eosinophils.

In this study, we defined an exacerbation episode as three consecutive days with respiratory symptoms requiring use of rescue medication or hospitalization. A defining feature of asthma is the daily variability of symptoms. The choice of 3 days was made to eliminate the inclusion of random fluctuation of symptoms as an exacerbation episode. This approach assured a consistent interpretation of the signs and symptoms that defined a true exacerbation. Sensitivity analysis using other cutoff levels

TABLE 1. PATIENT DEMOGRAPHICS, BASELINE CHARACTERISTICS AND HISTORY OF ATOPY, ASTHMA, AND ASTHMA MEDICATION USE

Characteristic	Montelukast (*n = 278*)	Placebo (*n = 271*)
Sex, n (%)		
Male	173 (62)	177 (65)
Female	105 (38)	94 (35)
Race, n (%)		
White	188 (68)	184 (68)
Asian	47 (17)	39 (14)
Black	2 (0.7)	1 (0.4)
Hispanic	40 (14)	43 (16)
Other	1 (0.4)	4 (1.5)
Age categories, n (%)		
< 36 mo	85 (31)	70 (26)
36–47 mo	94 (34)	95 (35)
48–59 mo	66 (24)	69 (26)
⩾ 60 mo	33 (12)	37 (14)
Age, median (range), mo	44 (24–72)	44 (24–72)
Daytime asthma symptom score*	n† = 276	n† = 269
median (range)	0.0 (0.0–0.7)	0.0 (0.0–0.9)
B-agonist use,‡ puffs/14 d	n† = 261	n† = 255
median (range)	0 (0–36)	0 (0–28)
Oral corticosteroid use for worsening asthma§, n (%)	n† = 277	n† = 271
⩽ 2 courses	247 (89)	257 (95)
⩾ 3 courses	30 (11)	14 (5)
Frequency of asthma symptoms‖, n (%)	n† = 278	n† = 270
⩽ 2 times/wk	231 (83)	235 (87)
> 2 times/wk	47 (17)	35 (13)
Nocturnal awakenings‖	n† = 278	n† = 271
⩽ 2 times/mo	226 (81)	235 (87)
> 2 times/mo	52 (19)	36 (13)
Positive RAST test, n (%)	n† = 265	n† = 264
	90 (34%)	94 (36%)

* Based on a 5-point scale; four domains (0 best to 4 worst) (maximum score 4).
† Number of patients with available information.
‡ Total number of treatments over 14 days of placebo run-in period.
§ Over the past year, relative to the first visit.
‖ Month before screening visit.

for number of days, symptoms score, and β-agonist use showed a similar treatment effect.

Viral-induced asthma exacerbations are seasonal, but seem to occur year-round outside the summer (20). Patients had few exacerbations and few or no asthma symptoms during the summer season in both groups for the Northern and Southern hemispheres; however, the treatment effect of montelukast was consistent throughout the rest of the year (Figure 5), suggesting that the treatment effect observed may have related to viral-induced exacerbations.

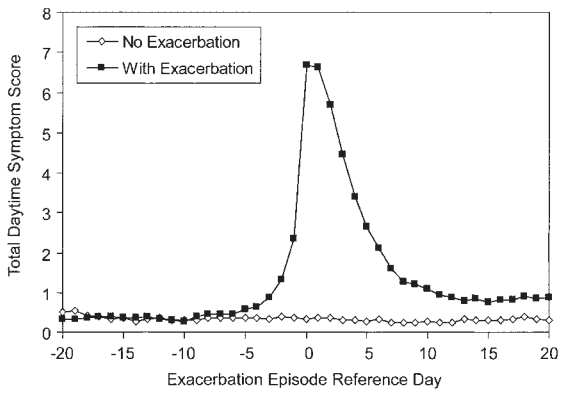

Figure 2. Mean total daytime symptoms score for all patients with and without an exacerbation. The first exacerbation episode was used for all patients having an exacerbation. *Open diamonds* = no exacerbation (n = 200); *filled squares* = with exacerbation (n = 322).

In an exploratory subanalysis within this study, viral identification, associated with symptoms, was performed in a subgroup of patients. The most frequently observed viruses were rhinoviruses followed by coronaviruses and respiratory syncytial virus. Rhinoviruses were the most common type of virus detected in nasal aspirates from children 9 to 11 years old with respiratory symptoms associated with viral infections (9). Slightly less than 50% of aspirates in our study were positive in contrast to approximately 80% positive in the previous study (9). The most likely explanation for this lower detection rate is suboptimal reporting and sampling in the present study compared with the previous one (9), because the present study was a multicenter one and there was no specific expertise in reporting on the children's part, nor in sampling on the investigators' part, whereas the previous study employed children previously trained in documenting and reporting such exacerbations and sampling was performed by highly trained and skilled investigators. It is also possible that some exacerbations were caused by triggers other than viral infections such as allergies. However, as indicated in the subgroup analysis, the treatment effect for patients with or without a history of allergic rhinitis was similar. The distribution of exacerbations episodes over the year was more consistent with viral exacerbations than allergy-related exacerbations. Although some exacerbations could be associated with allergies, the timing of the exacerbations over the year and the consistent effect in

TABLE 2. RATES OF EVENT PER YEAR, RELATIVE RATES AND PERCENT RATE REDUCTION FOR ASTHMA EXACERBATIONS AND OVERALL CORTICOSTEROID USAGE

	Montelukast (*n* = 265) Rate/yr* (95% CI)	Placebo (*n* = 257) Rate/yr* (95% CI)	Montelukast vs. Placebo		
			Relative Rate (95% CI)	Rate Reduction†	p Value
Asthma exacerbation					
Episodes	1.60 (1.35, 1.88)	2.34 (1.97, 2.79)	0.68 (0.56, 0.83)	31.9%	⩽ 0.001
Corticosteroid courses	1.19 (0.94, 1.51)	1.74 (1.39, 2.18)	0.68 (0.49, 0.95)	31.6%	0.024
Inhaled	0.66 (0.46, 0.94)	1.10 (0.83, 1.45)	0.60 (0.38, 0.94)	39.8%	0.027
Oral	0.53 (0.40, 0.70)	0.64 (0.47, 0.88)	0.82 (0.54, 1.25)	17.5%	0.368

Definition of abbreviation: CI = confidence interval.

* Average event rate estimated from Poisson regression model.

† Rate reduction = (1-relative rate) × 100.

patients with and without allergic rhinitis suggest that the majority of exacerbations were likely viral-induced.

As an incidental finding in the virus substudy, the number of common colds (criteria for nasal aspirate sampling) was reduced by 29% in the montelukast group (p = 0.07). This observation could be confounded by the treatment effect on exacerbations associated with an upper respiratory infection (e.g., exacerbations may increase the caregiver's attention to the symptoms). The rate of virus identification was similar in the two treatment groups. Future studies should explore if symptoms of common cold may be reduced by montelukast.

Recently, metapneumonia virus was detected in 20% of specimens from young children with acute respiratory illnesses for which no cause was previously found (21); however, in the present study, the rate of detection of metapneumovirus was very low (1%, Table 4), suggesting that in this population it was not a major contributor to viral- induced exacerbations.

It is possible that some patients had mild persistent asthma rather than intermittent asthma. However, such categories are somewhat arbitrary and children may move in and out of different severity groups (22, 23). The present study is a rigorous attempt to distill a large group of children with intermittent asthma. Patients were included in the study only if they were asymptomatic in the past 3 months and did not use β-agonists between exacerbation episodes. The inclusion criteria allowed randomization of patients with symptoms up to 4 days in 2 weeks during the run-in period. Up to 15% of patients had symptoms more than 2 times per week and 16% had nocturnal awakenings more than 2 times per month at baseline, which would place them in the mild persistent category according to the Global Initiative for Asthma (GINA) guidelines. However, patients with symptoms greater than 1.0 (average score on four daily daytime symptoms questions, range 0–5) on more than 2 consecutive days, and on more than a total of 4 days during the 2-week placebo run-in period did not qualify for the study. Therefore, most patients probably had intermittent asthma. In addition, no preventive therapy other than montelukast or placebo were allowed during the study and the number of exacerbations and the mean daily symptoms score were low throughout the year (Figure 2).

Patients in this clinical trial represent an age group and category of patients with asthma that are seldom studied. Airways inflammation is present in adults with intermittent asthma (24) and in children with mild asthma (25); however, it is not known if very young children with viral-induced intermittent asthma have similar inflammation. It is also not known whether intermittent asthma reflects a persistent mild form of asthma with rare symptoms or a separate entity such as viral-induced reactive airway disease. Consistent with the lack of clinical efficacy seen with inhaled steroid therapy in such patients, asthma guidelines

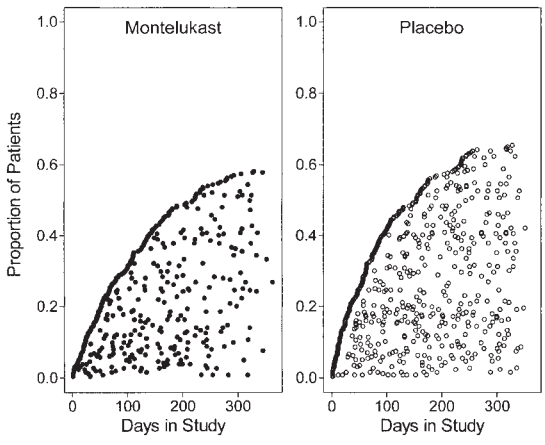

Figure 3. Individual exacerbation episode per patient over the entire study duration for montelukast (*filled circles*, *left*) and placebo (*open circles*, *right*). Patients were ordered by time to first exacerbation episode. Therefore, the *circles on the left* of each graph correspond to the start of the first exacerbation episode for the patient with the shortest time to first exacerbation episode. The circles that are more to the right correspond to the start of a possible second, third, etc., exacerbation episode.

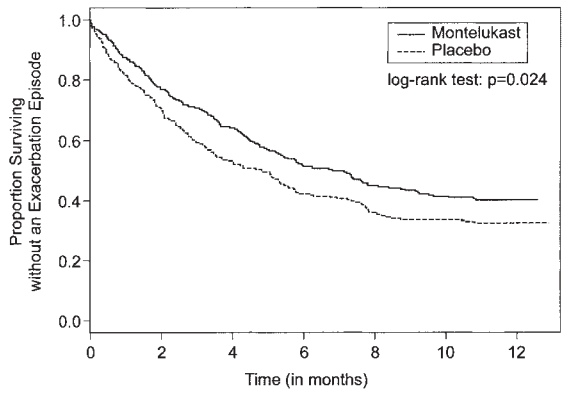

Figure 4. Kaplan-Meier estimate of the time to first asthma exacerbation episode over the 12-month study period. The time to the first exacerbation was significantly greater in the montelukast group compared with placebo (p = 0.024).

TABLE 3. ASSESSMENT OF TREATMENT EFFECT FOR EXACERBATION EPISODES FOR MONTELUKAST AND PLACEBO BY SUBGROUPS (NO SIGNIFICANT TREATMENT BY SUBGROUP INTERACTION WAS DETECTED)

	Montelukast		Placebo		
Subgroup*	n	Rate (Exacerbation Episode /yr)	n	Rate (Exacerbation Episode /yr)	Relative Rate† Estimate (95% CI)
Sex (p = 0.322)					
Male	166	1.69	166	2.28	0.74 (0.58, 0.95)
Female	99	1.58	91	2.63	0.60 (0.43,; 0.84)
Age categories (p = 0.895)					
< 36 mo	83	1.66	64	2.48	0.67 (0.47, 0.95)
36–47 mo	84	1.68	90	2.53	0.67 (0.47, 0.94)
48–59 mo	65	1.51	67	2.31	0.65 (0.43, 0.99)
⩾ 60 mo	33	1.81	36	2.15	0.84 (0.49, 1.46)
Race (p = 0.739)					
White	188	1.73	182	2.58	0.67 (0.53, 0.84)
Other	77	1.44	75	1.98	0.73 (0.49, 1.09)
History of atopic dermatitis (p = 0.842)					
Yes	78	1.89	83	2.82	0.67 (0.48, 0.94)
No	187	1.55	174	2.22	0.70 (0.55, 0.89)
History of allergic rhinitis (p = 0.766)					
Yes	85	1.70	88	2.37	0.72 (0.50, 1.03)
No	180	1.63	169	2.42	0.67 (0.53, 0.85)
Eosinophil count at baseline (p = 0.198)					
< median	115	1.79	126	2.84	0.63 (0.47, 0.84)
⩾ median	134	1.60	117	1.95	0.82 (0.61, 1.10)
β-agonist use at baseline (p = 0.662)					
< median	69	1.97	73	2.64	0.75 (0.51, 1.08)
⩾ median	187	1.54	172	2.28	0.67 (0.53, 0.86)
Number of positive RAST tests (p = 0.887)					
0	169	1.52	163	2.21	0.69 (0.53, 0.88)
⩾ 1	83	1.9	88	2.68	0.71 (0.50, 1.00)

Definition of abbreviation: CI = confidence interval.

* p value for treatment-by-subgroup interaction from a Poisson model with factors for treatment, subgroup, and treatment-by-subgroup interaction.

† Relative rate from Poisson regression model within each subgroup with factors for treatment and an offset for the number of days in the study.

do not provide guidance for preventive treatment. Although symptoms may be mild or absent outside times of exacerbation, asthma exacerbations are troublesome and the consequences of recurrent viral infections and resulting inflammation of the lower airways are unknown. However, a reduction in the number of exacerbation episodes and subsequent inflammation by montelukast in this study may lessen any impact that viral infections have on the course of the illness in addition to symptom relief. Although the results of this study were positive, it is not anticipated that mild intermittent pediatric patients would be treated daily with montelukast. The present findings prove the concept that montelukast reduced exacerbations in intermittent asthma, but it is not the claim of the study that management should necessarily apply year-round regular treatment. Because exacerbations were seasonal, therapy could begin before the viral season when the exacerbation rate is high. Alternately, length and

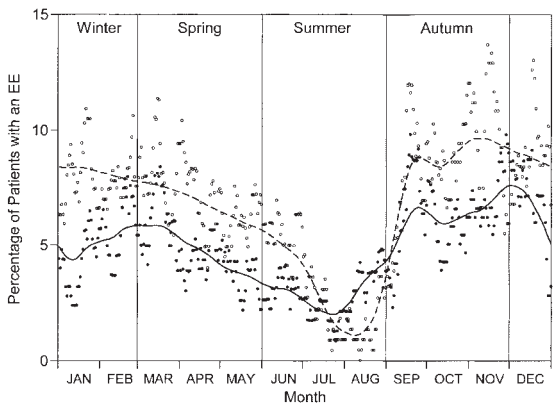

Figure 5. Daily percentage of patients with an exacerbation episode for the montelukast and placebo treatment groups. *Circles* indicate the percentage of patients having exacerbation episode at a specific calendar date. Calendar days, season, and months are represented for the Northern hemisphere (1 = January 1; 365 = December 31). For the Southern hemisphere, the calendar days are represented as 1 = July 1; 365 = June 30. *Solid lines*, *filled circles* = montelukast; *dashed lines*, *open circles* = placebo.

TABLE 4. NASAL ASPIRATE TESTS CONDUCTED AT EIGHT STUDY CENTERS

	Montelukast (*n = 46*)	Placebo (*n = 45*)*	Total (*n = 91*)
Number of nasal aspirates	65	93	158
All tests negative	27 (41.5%)	55 (59.1%)	82 (51.9%)
At least one test positive	38 (58.6%)	38 (40.8%)	76 (48.1%)
Rhinoviruses	24 (37.0%)	19 (20.1%)	43 (27.6%)
Coronaviruses	5 (7.8%)	9 (9.9%)	14 (9.0%)
Respiratory syncytial virus	5 (7.8%)	8 (8.8%)	13 (8.3%)
Influenza virus	4 (6.2%)	4 (4.4%)	8 (5.1%)
Enteroviruses	2 (3.1%)	2 (2.2%)	4 (2.6%)
Parainfluenza viruses	2 (3.1%)	1 (1.1%)	3 (1.9%)
Mycoplasma pneumoniae	1 (1.5%)	1 (1.1%)	2 (1.3%)
Adenoviruses	0 (0.0%)	1 (1.1%)	1 (0.6%)
Human metapneumovirus	0 (0.0%)	1 (1.1%)	1 (0.6%)
Chlamydia pneumoniae	0 (0.0%)	0 (0.0%)	0 (0.0%)

*One patient lost to follow-up.

initiation of therapy could be based on severity of symptoms and susceptibility experienced by a patient during exacerbation. Future studies should address the feasibility of beginning treatment at first signs of an upper respiratory infection in susceptible patients.

Studies evaluating the use of regular inhaled corticosteroids in children with viral-induced intermittent asthma, similar to the patient characteristics of the present study, showed that neither the rate nor the frequency of wheezing episodes changed with such therapy (6–8). The 32% reduction by montelukast seems clinically relevant and comparable to that seen in patients with asthma of a similar age. Knorr and colleagues treated 2- to 5-year-old patients with asthma with montelukast for 12 weeks (15). Poisson regression analysis of data from the Knorr study demonstrated that montelukast reduced asthma attacks by 24.5% (1.4 asthma attacks/year on montelukast versus 1.8 asthma attacks/year on placebo)—not unlike the reduction in exacerbation episodes in the current study. Asthma attacks (worsening asthma requiring rescue medication or asthma resource use) in the Knorr study (15) and exacerbations in the current study were evaluated similarly; therefore, the reduction is consistent.

Montelukast did not significantly alter the duration or severity of an asthma exacerbation after an episode occurred. The study was not designed to specifically investigate the effect of montelukast on these endpoints because patients were treated with other therapies during an asthma exacerbation. The action plan for worsening asthma may have led to some standardization of episode duration (e.g., patients were given corticosteroids routinely for predefined periods even if symptoms resolved earlier). Measurement of severity of an exacerbation episode also included such treatments. Therefore, the effect of montelukast on these endpoints could not be clearly defined in this trial.

In conclusion, montelukast significantly decreased the rate of asthma exacerbations and increased time to exacerbation in 2- to 5-year-old patients with asthma whose symptoms were intermittent. Consistent with these findings, the proportion of patients requiring inhaled corticosteroids or β-agonists were reduced by 30% and 40%, respectively, compared with placebo. This study is the first to demonstrate that exacerbations of mild intermittent asthma can be successfully treated with a controller agent. The results of this study should be confirmed, because they have broad implications for treatment of intermittent asthma in children where other conventional therapies have failed to show any clinical benefit.

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***Conflict of Interest Statement*:** H.B. has, within the last 3 years, received honoraria for lectures and attendance at pediatric Advisory Boards for Aerocrine, AstraZeneca (AZ), GlaxoSmithKline (GSK), Hoffman-La-Roche, Merck Sharpe and Dohme (MSD), Novartis, and Yamanouchi and owns world patents in the pharmaceutical industry in the respiratory field but receives no royalty. The Danish Pediatric Asthma Center has, in the last 3 years, received research grants from the following industry partners in increasing order: Aerocrine, MSD, GSK, and AZ; S.Z. received 5,200 Euros in 2004 for serving on an Advisory Board for MSD and has participated as a speaker in scientific meetings financed by MSD and, in 2003, received a research grant from MSD of 25,000 Euros; M.L.G.-G. is an employee of Merck & Company and holds stock options; S.L.J. has received grants to investigate mechanisms of the virus induced asthma from Merck ($200,000) and GSK ($1 million); L.G. is an employee of Merck & Company and holds stock options; J.M. is an employee of Merck & Company and holds stock options; C.A.T. is an employee of Merck & Company and holds stock options; P.P. is an employee of Merck & Company and holds stock options.

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