

This article was downloaded by: [Uppsala University Library]

On: 1 June 2009

Access details: Access Details: [subscription number 786945401]

Publisher Informa Healthcare

Informa Ltd Registered in England and Wales Registered Number: 1072954 Registered office: Mortimer House, 37-41 Mortimer Street, London W1T 3JH, UK



Journal of Asthma

Publication details, including instructions for authors and subscription information:

<http://www.informaworld.com/smpp/title~content=t713597262>

The Efficacy of Montelukast during the Allergy Season in Pediatric Patients with Persistent Asthma and Seasonal Aeroallergen Sensitivity

Nikolaos G. Papadopoulos ^a; George Philip ^b; Hilde Giezek ^b; Molly Watkins ^b; Steven S. Smugar ^b; Peter G. Polos ^b

^a Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece ^b Merck & Co., Inc., Whitehouse Station, New Jersey, USA

Online Publication Date: 01 May 2009

To cite this Article Papadopoulos, Nikolaos G., Philip, George, Giezek, Hilde, Watkins, Molly, Smugar, Steven S. and Polos, Peter G. (2009) 'The Efficacy of Montelukast during the Allergy Season in Pediatric Patients with Persistent Asthma and Seasonal Aeroallergen Sensitivity', *Journal of Asthma*, 46:4, 413 — 420

To link to this Article: DOI: 10.1080/02770900902847727

URL: <http://dx.doi.org/10.1080/02770900902847727>

PLEASE SCROLL DOWN FOR ARTICLE

Full terms and conditions of use: <http://www.informaworld.com/terms-and-conditions-of-access.pdf>

This article may be used for research, teaching and private study purposes. Any substantial or systematic reproduction, re-distribution, re-selling, loan or sub-licensing, systematic supply or distribution in any form to anyone is expressly forbidden.

The publisher does not give any warranty express or implied or make any representation that the contents will be complete or accurate or up to date. The accuracy of any instructions, formulae and drug doses should be independently verified with primary sources. The publisher shall not be liable for any loss, actions, claims, proceedings, demand or costs or damages whatsoever or howsoever caused arising directly or indirectly in connection with or arising out of the use of this material.

ORIGINAL ARTICLE

The Efficacy of Montelukast during the Allergy Season in Pediatric Patients with Persistent Asthma and Seasonal Aeroallergen Sensitivity

NIKOLAOS G. PAPADOPOULOS,^{1,*} GEORGE PHILIP,² HILDE GIEZEK,² MOLLY WATKINS,²
STEVEN S. SMUGAR,² AND PETER G. POLOS²

¹Allergy Department, 2nd Pediatric Clinic, University of Athens, Athens, Greece

²Merck & Co., Inc., Whitehouse Station, New Jersey, USA

Objective. To determine the effect of montelukast on asthma during the allergy season in children with persistent asthma and seasonal aeroallergen sensitivity. **Design.** This 3-week double-blind, placebo-controlled, parallel-group multicenter study compared daily montelukast 5 mg chewable tablets and placebo in patients 6–14 years of age with forced expiratory volume in 1 second (FEV₁) ≥ 60 and $\leq 85\%$ predicted, persistent asthma that is also active during allergy season, and documented sensitivity to seasonal allergens. Concomitant inhaled corticosteroid use was permitted in up to 40% of enrolled patients. The primary endpoint was the percentage change from baseline in FEV₁ over 3 weeks of treatment. Additional endpoints included the percentage change from baseline in β -agonist use, average changes in daytime and nighttime symptom score, AM and PM peak expiratory flow rate (PEFR), investigator's global asthma evaluation, and parent/guardian global asthma evaluation at the end of the treatment period. Adverse experiences (AEs) were collected to assess safety and tolerability. **Results.** A total of 421 patients were randomized to montelukast (N = 203) or placebo (N = 218). For the primary endpoint, the percentage change from baseline FEV₁, montelukast was not significantly different from placebo (least squares mean 9.53% vs. 9.15%, respectively; $p = 0.810$). Compared with placebo, montelukast was associated with significantly lower (better) investigator's global asthma evaluation (LS mean 2.71 vs. 2.98; $p < 0.05$) and parent/guardian global asthma evaluation (LS mean: 2.63 vs. 2.90; $p < 0.05$) scores. There were no significant differences between treatment groups for the other efficacy evaluations. Both treatments were well tolerated, with no significant differences observed in AE rates. **Conclusion.** Montelukast did not significantly improve FEV₁ compared with placebo over three weeks of treatment during the allergy season in pediatric patients with seasonal allergen sensitivity. (ClinicalTrials.gov identifier: NCT00289874)

Keywords asthma, global evaluation, montelukast, pollen, seasonal allergen sensitivity

This study was supported by Merck & Co., Inc. Merck & Co., Inc. provided montelukast and financial support to the conduct of the study. N.G.P. received grant support from Merck, GSK, and AstraZeneca; has been on advisory boards for Merck, GSK, AstraZeneca, Schering Plough, and UCB IotA; and has presented lectures for Merck, GSK, AstraZeneca, Schering Plough, and Novartis. G.P., H.G., P.G.P., and S.S.S.; and M.W. are or were employees of Merck & Co., Inc., who may potentially own stock and/or hold stock options in the Company.

N.G.P., G.P., H.G., S.S.S., and M.W. are responsible for the work described in this paper. All authors were involved in at least one of the following: conception, design, acquisition, analysis, statistical analysis, interpretation of data; and drafting the manuscript and/or revising the manuscript for important intellectual content. All authors provided final approval of the version to be published. P.P. was an employee of Merck & Co., Inc., and is currently employed by i3 Research in Basking Ridge, NJ, but continued to participate in authoring this manuscript.

Drs. Barbara Knorr, and Marie-Pierre Malice; and Joanne Woodland and Sheila Erespe were involved with at least one of the following but did not meet all criteria for authorship: conception, design, data acquisition, data analysis (including statistical analysis), or interpretation of the data; administrative, technical, or material support; critically reviewed the study proposal, abstracted charts, or served as scientific advisors.

*Corresponding author: Nikolaos G. Papadopoulos, As. Professor in Pediatric Allergology, Head, Allergy Department, 2nd Pediatric Clinic, University of Athens, 41, Fidiopidou, Athens 115 27; Greece; E-mail: ngp@allergy.gr

INTRODUCTION

The prevalence of asthma is still increasing in most of the world (1), and although important progress has been made in the past years in its understanding and treatment, asthma is still not well controlled in the majority of patients who have it (2). The clinical presentation of paediatric asthma is variable and, although there are overlaps, different phenotypes can be distinguished according to the major trigger of symptoms, including allergen-induced asthma (3).

Cysteinyl leukotrienes are important mediators of inflammation in asthma and allergic rhinitis (4). They have been shown to be involved in the activation and migration of effector cells to the bronchial mucosa in response to allergen, the modulation of airway smooth muscle function (5), and they were recently associated with reticular membrane thickening (i.e., remodeling) in children with moderate to severe disease (6).

Several studies have confirmed that montelukast, a leukotriene receptor antagonist, is effective in the treatment of chronic asthma and allergic rhinitis in both adults and children (7). Efficacy has specifically been demonstrated in adult asthmatics with allergen sensitization and corresponding seasonal asthma activity (8). The latter finding has not yet been reproduced in children.

The aim of this study was to evaluate the effectiveness of montelukast versus placebo in improving lung function and controlling disease activity during the allergy season in

children with seasonal aeroallergen sensitivity and persistent asthma also active during the season.

METHODS

The protocol (Merck protocol 336) was approved by an institutional review board at each site, and written informed consent was obtained from all patients and their parents or legal guardians before enrollment. To oversee this study a Scientific Advisory Committee (SAC) was established comprising an international panel of asthma and allergy specialists and Merck & Co., Inc., clinical research professionals. The role of the SAC was to develop and refine the primary and secondary hypotheses, design the study protocol, formulate the statistical analysis plan, analyze and interpret the study findings, and develop the final report and all related publications.

Patients

Eligible patients were 6 to 14 years of age, with a history of persistent asthma (duration ≥ 1 year) also active during allergy seasons, and documented sensitivity to seasonal aeroallergens. Aeroallergen sensitivity was determined by a positive skin test (wheal ≥ 3 mm greater than saline control) to at least two geographically relevant seasonal aeroallergens at visit 1 or within the preceding year. Testing included at least three tree, two grass, and two weed allergens. Eligible patients began a 1-week single-blind placebo run-in period, at the end of which they were required to have a daytime asthma symptom score sum of at least 11 (three questions on a daily 0-to-6 scale), average short-acting β -agonist use ≥ 1 puff daily, forced expiratory volume in one second (FEV₁) $\geq 60\%$ and $\leq 85\%$ predicted, and reversible airway obstruction (FEV₁ increase $\geq 12\%$ between 20 to 30 minutes after inhaled β -agonist administration). The first 40% of patients randomized into the study who were currently taking a stable dose of inhaled corticosteroid (ICS) monotherapy for at least 1 month were allowed to continue their medication throughout the study if they remained at the same dose. Patients taking a stable dose of nasal cromolyn or oral antihistamines for at least 2 weeks, or receiving allergy shots for 6 months were permitted to enter the study and were required to continue on the same dose throughout the study period. As-needed short-acting inhaled β -agonist (albuterol) use was permitted, but routine use in the absence of symptoms was discouraged. Patients were excluded if they had taken oral, intravenous, intramuscular, or intra-articular corticosteroids within 1 month; nasal corticosteroids within 10 days; ICS combined with another asthma medication (e.g., long-acting β -agonists); leukotriene receptor antagonists or inhaled cromolyn or nedocromil within 10 days; oral or long-acting β -agonists or inhaled anticholinergic agents within 10 days; theophylline within 10 days; or intravenous gammaglobulin or immunosuppressants within 1 month of the prescreen visit. Other exclusion criteria included previous intubation for asthma; hospitalization for asthma within 3 months, or asthma treated in an emergency room within 1 month; unresolved signs or symptoms of an upper respiratory tract infection within 3 weeks of the placebo run-in period; or plans to move or vacation outside of home geographic area for more than 2 days during the study period.

Study Design

This was a randomized, multicenter, double-blind, placebo-controlled, parallel-group study performed at 103 sites in the United States from March 2006 to June 2007 during the spring and fall allergy seasons. The study was originally designed to be conducted during a single season but, owing to slow recruitment during Spring 2006, was continued through the Fall 2006 and Spring 2007 seasons. The study comprised five visits: following a screening period, patients entered a 1-week, single-blind placebo run-in period (period 1, starting at visit 1), during which baseline asthma symptom scores, compliance, and β -agonist use were determined, electronic diary instruction was reviewed, and skin testing was performed if not performed within the previous year. Patients returned at the end of the run-in period (period II, ending at visit 2), and eligible patients were randomized to montelukast 5 mg chewable tablet or matching placebo once daily at bedtime for 3 weeks (period 3, ending at visit 3) according to a computer-generated allocation schedule. Numbered containers were used to implement allocation. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel, remained blinded to treatment allocation throughout the study; the code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete. Patients were stratified according to their ICS use (yes/no). Pollen levels (measured as a semi-quantitative index) were collected daily for each site during the three seasons of active enrollment from www.pollen.com, and included major pollens (up to three) in the area.

Patients performed peak expiratory flow rate (PEFR) measurements each morning before using any medication and in the evening before taking study medication and at least 4 hours after the last albuterol dose. An electronic diary was used to capture AM and PM PEFR, albuterol use, and daily daytime and nighttime asthma symptom scores. Patients 9 to 14 years of age entered data themselves; parents/guardians of patients 6 to 8 years of age entered the data after asking their children the diary questions.

At any time during periods 1 to 3, patients whose PEFR fell below 60% of their personal best at prescreening, visit 1, or visit 2, or those with a significant worsening of asthma symptoms necessitating use of more than 8 inhalations of short-acting β -agonist daily, were instructed to contact the investigator. If, in the opinion of the investigator, patients required prohibited therapy, they were discontinued from the study and given the appropriate therapy. Diary data, adverse experiences (AEs), vital signs, and parent/guardian and investigator global assessments were collected at the discontinuation visit (visit 3). An additional telephone contact was made 14 days following discontinuation to assess any new or continuing serious AEs.

Efficacy and Safety Endpoints

The primary efficacy endpoint was the percentage change in FEV₁ after 3 weeks of treatment compared with baseline (randomization or the last value obtained before the treatment period). The secondary efficacy endpoint was the percentage change from baseline after 3 weeks in mean daily as-needed albuterol use. Additional efficacy endpoints included the

average change from baseline after 3 weeks in mean daytime asthma score (determined by three questions regarding trouble breathing, asthma bothersomeness, and activity limitation, each scored on a worsening categorical scale from 0 to 6), mean nighttime asthma score (determined by asthma-related awakening: "no," "once," "more than once," "awake all night"), AM PEFR, PM PEFR, and parent/guardian and investigator asthma global assessment (each measured on a 0-to-6 scale from "very much better" to "very much worse").

Prespecified subgroup analyses of the primary endpoint were performed for the variables of gender, age (<9 years/≥9 years), race (white/black/other), asthma severity (baseline FEV₁ above/below median), pollen levels (above/below median levels observed), inhaled steroid monotherapy user at entry (yes/no) and season (spring 2006, fall 2006, spring 2007).

Post-hoc analyses evaluated the primary and secondary endpoints and the tertiary global evaluation endpoints by concurrent antihistamine use. An additional post-hoc analysis was performed to evaluate asthma exacerbations using a definition similar to that used in a previous study of montelukast in pediatric asthma (9): a day with any one of the following: (1) decreased AM PEFR >20% and AM PEF at least 180 L/min; (2) increased β-agonist use over 70% and a minimum increase of at least 2 puffs; (3) increased daytime asthma symptom score over 50%; (4) "awake all night" on nighttime asthma symptom score; or (5) hospitalization, emergency room visit, or treatment with oral, intravenous, or intramuscular corticosteroids for asthma.

The incidence of overall AEs, serious AEs, drug-related AEs, and discontinuation because of AEs was recorded to evaluate tolerability and safety.

Statistical Analysis

The primary hypothesis was that montelukast 5 mg chewable tablet administered once daily over 3 weeks in patients 6 to 14 years of age with persistent asthma and seasonal aeroallergen sensitivity will demonstrate superior improvement in FEV₁ compared with placebo. The primary efficacy analysis was based on the full analysis set population (i.e., all randomized patients who received double-blind study drug and had a baseline and on-treatment value for analysis available). A per-protocol analysis excluding patients with important protocol violations was also performed. The primary endpoint was analyzed using an analysis of variance (ANOVA) model that included factors for treatment, season (spring 2006, fall 2006, spring 2007), and ICS use at entry (yes/no). Because of a non-normal distribution of the secondary endpoint, the percentage change from baseline mean daily as-needed albuterol was analyzed using a nonparametric method with an ANOVA model on the Tukey's normalized ranks. The tertiary endpoints of global assessments were analyzed using the same model as the primary endpoint. The remaining tertiary diary endpoints were analyzed using an analysis of covariance (ANCOVA) model using the corresponding baseline as a covariate and included factors for treatment, season, and ICS use.

With 225 patients per group, there was 90% power to detect a significant difference of 5% (2-sided $\alpha = 0.05$) between montelukast and placebo for the primary endpoint, assuming

a standard deviation (SD) of 15% and 80% power to detect a difference of 4% under the same assumptions. Because of recruitment difficulties, the planned sample size was reduced to 200 evaluable patients per treatment group. A somewhat increased variability was expected owing to the extension of the study over three seasons (two spring and one fall). Assuming an SD of 16%, a sample of 200 patients per treatment group provides 80% power at $\alpha = 0.05$ (two-sided test) to detect a 4.6% difference between treatment groups. Because (1) there was only a single comparison for the primary efficacy endpoint; (2) the secondary variable was only tested if the primary was significant; and (3) the other comparisons were supportive in nature, no adjustment for multiplicity was necessary.

All randomized patients who received the study drug were included in the safety analysis. Treatment groups were compared using Fisher's exact test on the overall incidence of AEs, serious AEs, drug-related AEs, and discontinuations due to AEs.

RESULTS

Patients

A total of 421 patients were randomized to montelukast (N = 203) or placebo (N = 218) (Figure 1). Approximately 97% of patients in each group completed the study. The most common reasons for discontinuation were deviation from protocol in the montelukast group (1.5%), and clinical AE (2.3%) in the placebo group. Baseline patient characteristics are summarized in Table 1. The majority of patients were white (~47%) and male (~60%) and had mean age of approximately 10.8 years. Approximately 22% of patients in

TABLE 1.—Patient baseline characteristics.

	Montelukast 5 mg (N = 203)	Placebo (N = 218)
Gender, n (%)		
Female	81 (39.9)	90 (41.3)
Male	122 (60.1)	128 (58.7)
Age, years		
Mean (SD)	10.6 (2.4)	10.7 (2.4)
< 9 years n (%)	59 (29.1)	57 (26.1)
≥ 9 years n (%)	144 (70.9)	161 (73.9)
Race, n (%)		
White	94 (46.3)	104 (47.7)
Black	60 (29.6)	66 (30.3)
Hispanic American	40 (19.7)	40 (18.3)
Other	9 (4.4)	8 (3.7)
Season of enrollment, n (%)		
Spring 2006	82 (40.4)	90 (41.3)
Fall 2006	56 (27.6)	50 (22.9)
Spring 2007	65 (32.0)	78 (35.8)
Concomitant inhaled corticosteroid use,* n (%)	43 (21.2)	51 (23.4)
Concomitant antihistamine use,* n (%)	44 (21.7)	46 (21.1)
History of allergic rhinitis, n (%)	111 (54.7)	119 (54.6)
FEV ₁ (L), mean (SD)	1.81 (0.57)	1.84 (0.60)
% predicted FEV ₁ , mean (SD)	77.4 (7.5)	77.7 (7.5)
β-agonist use, mean puffs/day (SD)	3.0 (1.8)	2.7 (1.7)
AM PEFR, mean L/min (SD)	260.2 (88.4)	260.6 (87.1)
PM PEFR mean L/min (SD)	269.1 (90.3)	270.4 (88.6)
Daytime asthma symptom score†, mean (SD)	1.8 (1.0)	1.6 (1.0)

*Use during the treatment period.

†Average of three questions scored on a worsening scale of 0 to 6.

FEV₁ = forced expiratory volume in 1 second; PEFR = peak expiratory flow rate; SD = standard deviation.

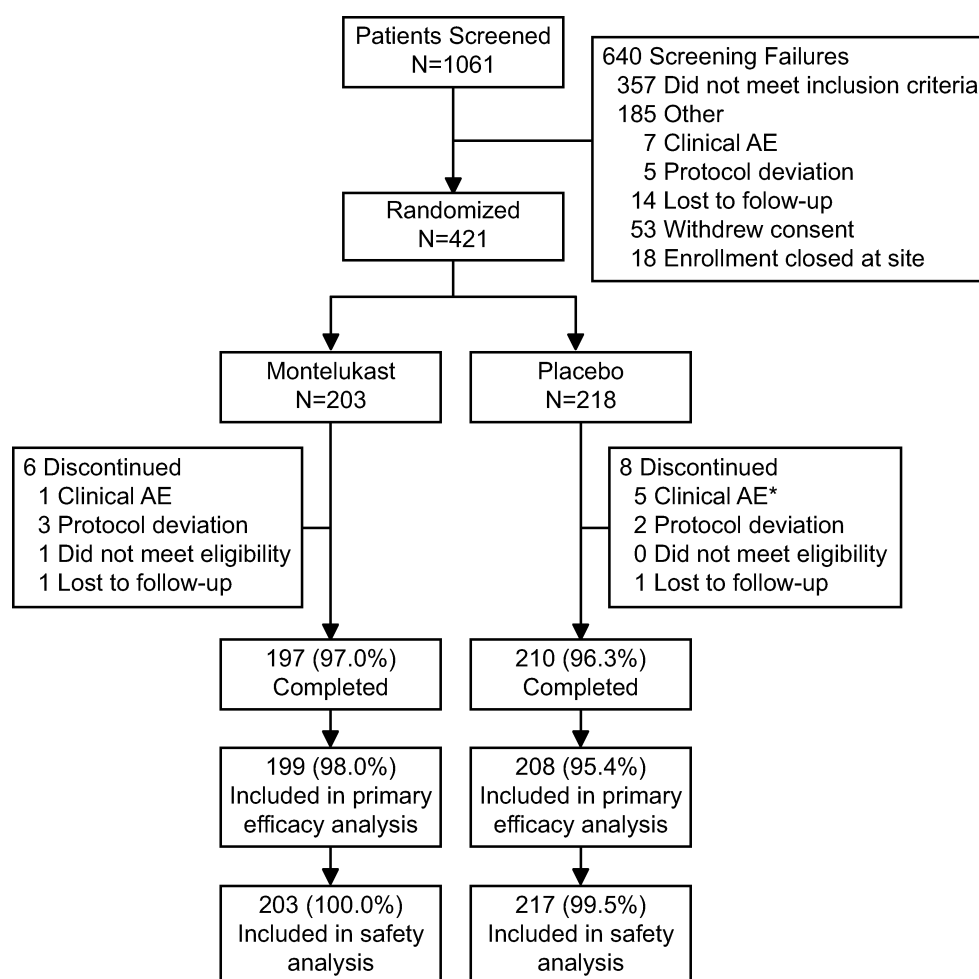


FIGURE 1.—Patient flow through the study. *One patient discontinued due to a clinical adverse experience (AE) never received any study drug.

the study were receiving concomitant ICS, and 21% were taking concomitant systemic antihistamines. The mean percent predicted FEV₁ was approximately 77%. Enrollment was highest in the spring 2006 season (~40% of total enrollment). Overall, baseline characteristics were generally similar between treatment groups.

Efficacy

For the primary endpoint of percentage change from baseline FEV₁, there was no significant difference between montelukast and placebo (LS mean: 9.53% vs. 9.15%,

respectively; difference: 0.38% [95% CI: -2.74, 3.50]; $p = 0.810$) (Table 2). There were no significant differences between treatment groups in the analyses of the primary endpoint by prespecified subgroups (Figure 2); treatment difference was consistent among subgroups for gender, age, race, concomitant inhaled steroid use, asthma severity, and pollen level. A somewhat higher treatment difference was observed for the subgroup spring 2007 (treatment difference in LS means of 2.52%).

There were no significant differences between treatments for the secondary endpoint of percentage change from

TABLE 2.—Changes from baseline in primary, secondary, and tertiary endpoints.*

	Montelukast 5 mg	Placebo	<i>p</i> value
FEV ₁ (percent change from baseline)	9.53 (7.05, 12.01)	9.15 (6.71, 11.59)	0.810
Mean daily β -agonist use (percent change from baseline), median (SD) [†]	-18.88 (84.75)	-12.40 (53.88)	0.173
Daytime asthma score	-0.23 (-0.33, -0.13)	-0.27 (-0.37, -0.17)	0.562
Nighttime asthma symptom score [‡]	-0.21 (-0.30, -0.13)	-0.20 (-0.30, -0.10)	0.788
AM PEFR	7.18 (1.89, 12.48)	7.32 (2.19, 12.45)	0.968
PM PEFR	4.32 (-0.93, 9.57)	5.61 (0.51, 10.70)	0.700

CI = confidence interval; FEV₁ = forced expiratory volume in 1 second; PEFR = peak expiratory flow rate; SD = standard deviation.

*All values least squares means (95% CI) unless otherwise noted.

[†] Nonparametric results.

[‡] Patients having at least two awakenings per week at baseline.

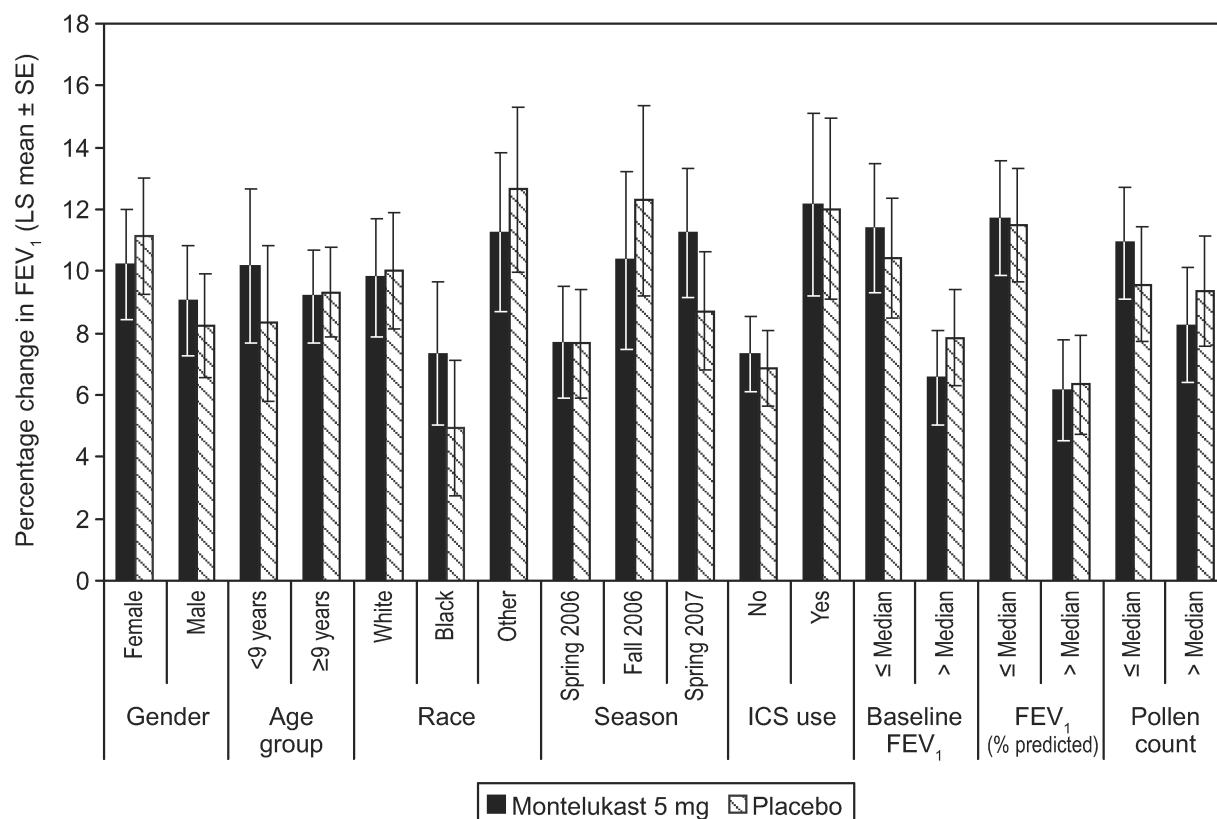


FIGURE 2.—Prespecified subgroup analysis of primary endpoint. LS = least squares; SE = standard error.

baseline in mean daily β -agonist use or tertiary endpoints of average daytime asthma score, nighttime asthma score, AM PEF, or PM PEF (Table 2). Montelukast was significantly more effective than placebo for the investigator's global asthma evaluation (LS mean: 2.71 vs. 2.98; $p < 0.05$) (Figure 3A) and parent/guardian global asthma evaluation (LS mean: 2.63 vs. 2.90; $p < 0.05$) (Figure 3B).

Post-hoc analyses

The post-hoc analyses of endpoints as a function of antihistamine use did not reveal any significant treatment differences (data not shown), nor was any between-treatment difference observed in the percentage of days of worsening asthma (Table 3).

Safety

Both treatments were well tolerated, and there were no significant differences in AE rates between treatment groups

(Table 4). There were no serious AEs in the montelukast group and four in the placebo group. Two patients reported serious AEs of asthma, one patient reported overdose, and one patient reported respiratory distress and femur fracture. None of the serious AEs was considered to be drug-related.

DISCUSSION

The purpose of the present study was to evaluate the effect of montelukast on asthma, as measured by FEV₁, in children who had asthma that was active during the allergy season and who had documented seasonal aeroallergen sensitivity. In this study, montelukast did not significantly improve FEV₁ compared with placebo. Prespecified subgroup analyses also did not demonstrate significant treatment differences in FEV₁. For the secondary endpoint of change in mean daily β -agonist use, and the tertiary endpoints of daytime and nighttime asthma symptom score, and AM and PM

TABLE 3.—Episodes of worsening asthma.

	Montelukast 5 mg	Placebo	<i>p</i> value
Percentage of days with asthma exacerbations, mean (SD)	14.8 (22.6)	15.6 (21.0)	0.202
Percentage of patients with an asthma exacerbation day	55.7	63.0	NA

NA = not applicable; SD = standard deviation.

TABLE 4.—Clinical adverse experiences.

	Montelukast 5 mg N = 203 n (%)	Placebo N = 217 N (%)
Clinical AE	17 (8.4)	23 (10.6)
Drug-related AE	2 (1.0)	2 (0.9)
Serious AE	0 (0.0)	4 (1.8)
Discontinuation due to AE	1 (0.5)	4 (1.8)

AE = adverse experience.

*Determined by the investigator to be possibly, probably, or definitely drug related.

Although a patient may have two or more AEs, the patient is counted only once in a category or overall.

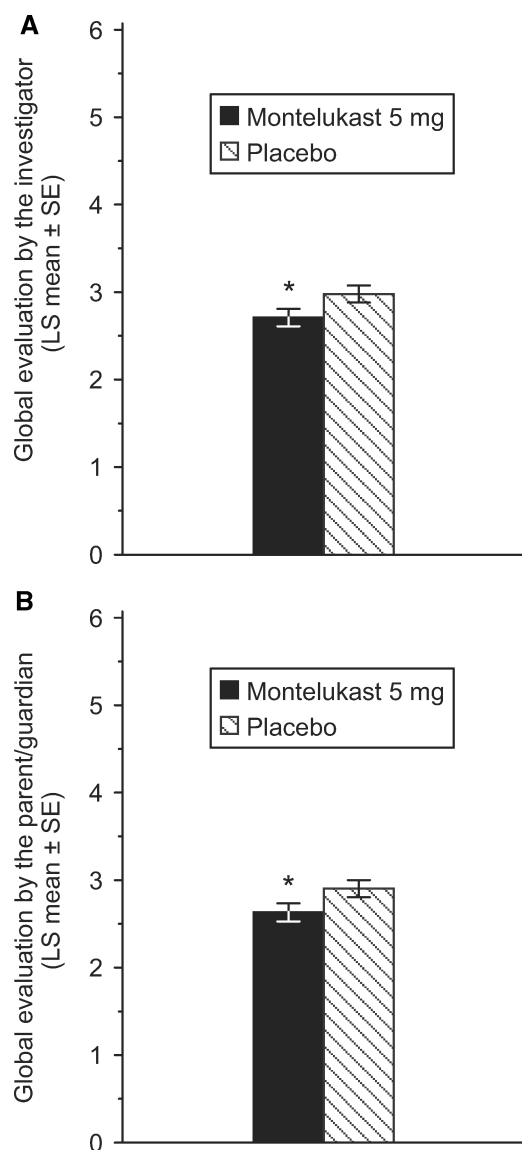


FIGURE 3.—Global evaluations. (A) Global evaluation by the investigator; (B) Global evaluation by the parent/guardian. A lower score is better. * $p < 0.05$ compared with placebo. LS = least squares; SE = standard error.

PEFR, significant treatment differences were not observed. There were significant improvements in patients receiving montelukast, compared with placebo, in both the investigator's and the parent/guardian's global asthma evaluations.

These findings are unexpected as montelukast is known to be efficacious for pediatric asthma (9). Moreover, in a study similar to the present study, Busse et al. (8) found that, in adults who had asthma that was active during the allergy season and who had documented seasonal aeroallergen sensitivity, montelukast was significantly more effective in improving daytime asthma symptoms score, β -agonist use, nighttime symptoms, and PEFR. However, FEV₁ was not an efficacy endpoint in the study by Busse et al.

There are a number of possible explanations for our findings. First, and most importantly, the present study had a large placebo response, particularly in comparison to the

study from Knorr et al. (9), an 8-week efficacy study, comparing montelukast and placebo in children 6 to 14 years of age, on which our planned sample size was based. The placebo-group percentage change from baseline in FEV₁ in this study (+9.2%) far exceeded the placebo group change in the Knorr study (+3.6%). Furthermore, the placebo-group percentage change for β -agonist use was strikingly different in this study (improving by –12.4% over the 3 weeks of study treatment) from that in the Knorr study (worsening by +9.6% over 8 weeks). In contrast, the montelukast group percentage change in FEV₁ in this study (+9.5%) was similar to the change in the Knorr study (+8.2%), and the montelukast effect on β -agonist use was also more similar between our study (–18.9%) and the Knorr study (–12.6%) (9).

The placebo response in asthma has been well described, including effects on objective measures (10–12). The exact cause for the robust response in our study is unclear, but it may be related to both a population with less severe asthma as well as a relatively mild level of seasonal allergen exposures. For example, our post-hoc analysis of episodes of worsening asthma, using a definition similar to that of Knorr et al. (9), did not show a significant difference between the two treatment groups. However, it is notable that only 55.7% of patients in the montelukast group and 63.0% of patients in the placebo group experienced asthma exacerbation days, compared with 95.5% and 84.8%, respectively, in the study by Knorr et al. (9). These results suggest somewhat milder disease in our subjects compared with those in the Knorr study. Indeed, patients in our study had higher FEV₁ percent predicted (77% vs. 72%), less β -agonist use (2.9 vs. 3.3 puffs/day), and less ICS use (22% vs. 36%) at baseline, all of which suggest a population with less severe asthma in our study versus the Knorr study, which may have reduced the ability to show a significant improvement with active treatment. Moreover, the mean baseline daytime asthma symptom score (on a scale of 0 to 6) was 1.8 in the montelukast group and 1.6 in the placebo group. Thus, despite the baseline FEV₁ and β -agonist use in our patients, which suggests more moderate disease, the symptom scores were relatively mild.

It is also possible these results reflect the relatively mild allergy seasons in the present study (data unavailable), which may have been insufficient to induce seasonal allergic asthma worsening to a degree that would be detected by this study. For instance, a study by Chervinsky et al. (13) comparing montelukast and placebo in allergic rhinitis found a significant interaction between treatment effect and level of pollen exposure, with less montelukast effect and greater placebo effect in patients who were randomized during times of low pollen levels. Moreover, they found enhanced response to placebo in patients exposed to low and decreasing pollen levels. In our study, pollen levels (as collected by and categorized by www.pollen.com [14]) were classified as “medium” (4.9 to 7.2 on a scale of 0 to 12) at the beginning of the season and decreased thereafter. Levels were considerably lower in the fall 2006 season than in the spring 2006 or spring 2007 seasons. Although we did not observe any significant treatment difference or interaction by pollen count or season, our results are somewhat similar to those of Chervinsky et al. (13): The greatest effect of placebo relative to montelukast was seen in the season with the lowest pollen count (i.e., fall 2006), although this relationship was not entirely consistent.

It is therefore possible that the generally mild exposure levels may partially account for the results of this study, especially regarding the strong placebo response.

We categorized allergen sensitivities to either tree, weed, grass, or other (e.g., dust mite), the distribution of which was similar between treatment groups (data not shown). However, it is still possible that there is some disparity in specific allergen sensitivities (e.g., cedar vs. redwood). Because different allergens have different peaks and durations (15, 16), disparities in specific allergens between treatment groups may have affected the outcome of this study.

Patients in the present study received medication at the start of allergy season, by which time underlying inflammatory response may have already begun, making it more difficult to show an effect after only 3 weeks of treatment. It is possible that treatment initiated before the allergy season would have shown a greater difference between montelukast and placebo. Indeed, Johnston et al. (17) evaluated the efficacy of montelukast or placebo administered on September 1 in reducing annual autumn peak in asthma morbidity in children associated with the return to school (i.e., the "September epidemic"). They found that montelukast significantly reduced asthma exacerbations and unscheduled physician visits for asthma, compared with placebo, when administered prophylactically at the beginning of the school year.

Finally, it is possible that our findings represent natural disease variability, which may be particularly variable in children with asthma (18) versus adults with asthma (as in the study by Busse et al.). It is notable that the Knorr study required patients to demonstrate airway reversibility $\geq 15\%$ after β -agonist administration on two separate visits during the pre-randomization run-in period (9). By contrast, our study required only a single demonstration of reversibility of $\geq 12\%$. Thus, it is possible that patients in the Knorr study had less variable (and more severe) disease than patients in our study, which is supported by the baseline asthma measures previously noted.

In the present study, montelukast was associated with significantly greater investigator's and parent's/guardian's global evaluation scores, compared with placebo, despite the lack of significant treatment differences in other objective and subjective measures. One possible explanation for these seemingly incongruent findings is that global evaluations generally take into account quality of life and other issues not necessarily captured by lung function measurements or symptoms, (19–22) particularly in patients with more mild asthma (23). It is also possible that, in this population of patients with known seasonal aeroallergen sensitivity, more than half of whom had a history of allergic rhinitis, these scores may reflect improvements in upper airway disease that were not otherwise quantified in this study but have been well demonstrated in other studies of montelukast for allergic rhinitis (24–29). Finally, it is possible that these measures can be more sensitive to change than either lung function or symptom scores. It is notable that montelukast has been shown to improve asthma symptoms and other indices of severity without having a significant effect on FEV₁ in adults with mild asthma (30).

The present study has several limitations. First, as noted, because of recruitment difficulties, the study was conducted in three seasons rather than one, and enrolled fewer patients

than originally planned. Although we did not observe any significant interaction between treatment and season, the variability in allergen levels between the seasons and the smaller sample size in each season may have affected our results. Second, we did not collect data on upper airway symptoms. Given the patients' history of aeroallergen sensitivity and allergic rhinitis, and given the significant difference in global evaluations in the montelukast group but nonsignificant differences in other evaluations, such information might provide further insight into reconciling these results. Finally, obtaining quantitative pollen grain counts rather than a general index of categorized severity of pollen levels would have been more useful to allow descriptions of pollen season severity using more scientifically relevant and analyzable exposure levels.

In conclusion, montelukast was not more effective than placebo in improving FEV₁ over 3 weeks of treatment in children with asthma and seasonal aeroallergen sensitivity during the allergy season in this study population. These results appear to be driven, at least in part, by a large placebo response compared with previous findings as well as a more mild asthma patient population than predicted from past studies and relatively low pollen indices. Montelukast was significantly more effective than placebo for patient and physician global evaluations.

ACKNOWLEDGMENT

The authors thank Barbara Knorr, M.D., for her critical review of the manuscript. They also thank Marie-Pierre Malice, Ph.D., for her contributions to the statistical analyses, Joanne Woodland for her contributions to the conduct of the study, and Sheila Erespe for her assistance with the preparation of the manuscript. They would also like to acknowledge the contributions of John O. Warner, M.D., and the late Gail Shapiro, M.D., F.A.A.A.I., who were members of the Protocol 336 Scientific Advisory Committee.

REFERENCES

1. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, Williams H. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006; 368:733–743.
2. Rabe KF, Adachi M, Lai CK, Soriano JB, Vermeire PA, Weiss KB, Weiss ST. Worldwide severity and control of asthma in children and adults: the global asthma insights and reality surveys. *J Allergy Clin Immunol* 2004; 114:40–47.
3. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills T, Pohunek P, Simons FE, Valovirta E, Wahn U, Wildhaber J. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008; 63:5–34.
4. Bisgaard H. Pathophysiology of the cysteinyl leukotrienes and effects of leukotriene receptor antagonists in asthma. *Allergy* 2001; 56 (suppl 66):7–11.
5. Parameswaran K, Radford K, Fanat A, Stephen J, Bonnans C, Levy BD, Janssen LJ, Cox PG. Modulation of human airway smooth muscle migration by lipid mediators and Th-2 cytokines. *Am J Respir Cell Mol Biol* 2007; 37:240–247.
6. Lex C, Zacharasiewicz A, Payne DN, Wilson NM, Nicholson AG, Kharitonov SA, Barnes PJ, Bush A. Exhaled breath condensate cysteinyl leukotrienes and airway remodeling in childhood asthma: a pilot study. *Respir Res* 2006; 7:63.

7. Storms W. Update on montelukast and its role in the treatment of asthma, allergic rhinitis and exercise-induced bronchoconstriction. *Expert Opin Pharmacother* 2007; 8:2173–2187.
8. Busse WW, Casale TB, Dykewicz MS, Meltzer EO, Bird SR, Hustad CM, Grant E, Zeldin RK, Edelman JM. Efficacy of montelukast during the allergy season in patients with chronic asthma and seasonal aeroallergen sensitivity. *Ann Allergy Asthma Immunol* 2006; 96:60–68.
9. Knorr B, Matz J, Bernstein JA, Nguyen H, Seidenberg BC, Reiss TF, Becker A. Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. *Pediatric Montelukast Study Group. JAMA* 1998; 279:1181–1186.
10. Kemeny ME, Rosenwasser LJ, Panettieri RA, Rose RM, Berg-Smith SM, Kline JN. Placebo response in asthma: a robust and objective phenomenon. *J Allergy Clin Immunol* 2007; 119:1375–1381.
11. Leigh R, MacQueen G, Tougas G, Hargreave FE, Bienenstock J. Change in forced expiratory volume in 1 second after sham bronchoconstrictor in suggestible but not suggestion-resistant asthmatic subjects: a pilot study. *Psychosom Med* 2003; 65:791–795.
12. Joyce DP, Jackevicius C, Chapman KR, McIvor RA, Kesten S. The placebo effect in asthma drug therapy trials: a meta-analysis. *J Asthma* 2000; 37:303–318.
13. Chervinsky P, Philip G, Malice MP, Bardelas J, Nayak A, Marchal JL, van Adelsberg J, Bousquet J, Tozzi CA, Reiss TF. Montelukast for treating fall allergic rhinitis: effect of pollen exposure in 3 studies. *Ann Allergy Asthma Immunol* 2004; 92:367–373.
14. Frequently asked questions about pollen forecasting and sampling for allergy alerts. Available at <http://pollen.com/allergy-hay-fever-faq.asp>. Accessed October 8, 2008.
15. D'Amato G, Cecchi L, Bonini S, Nunes C, Annesi-Maesano I, Behrendt H, Liccardi G, Popov T, van Cauwenberge P. Allergenic pollen and pollen allergy in Europe. *Allergy* 2007; 62:976–990.
16. Tobias A, Galan I, Banegas JR, Arangues E. Short term effects of airborne pollen concentrations on asthma epidemic. *Thorax* 2003; 58:708–710.
17. Johnston NW, Mandhane PJ, Dai J, Duncan JM, Greene JM, Lambert K, Sears MR. Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics* 2007; 120:e702–712.
18. Chipps BE, Spahn JD, Sorkness CA, Baitinger L, Sutton LB, Emmett AH, Dorinsky PM. Variability in asthma severity in pediatric subjects with asthma previously receiving short-acting beta2-agonists. *J Pediatr* 2006; 148:517–521.
19. Juniper EF, Svensson K, O'Byrne PM, Barnes PJ, Bauer CA, Lofdahl CG, Postma DS, Pauwels RA, Tattersfield AE, Ullman A. Asthma quality of life during 1 year of treatment with budesonide with or without formoterol. *Eur Respir J* 1999; 14:1038–1043.
20. Carranza R, Jr, Edwards L, Lincourt W, Dorinsky P, ZuWallack RL. The relationship between health-related quality of life, lung function and daily symptoms in patients with persistent asthma. *Respir Med* 2004; 98:1157–1165.
21. Luskin AT. What the asthma end points we know and love do and do not tell us. *J Allergy Clin Immunol* 2005; 115:S539–S545.
22. Bukstein D, Kraft M, Liu AH, Peters SP. Asthma end points and outcomes: what have we learned? *J Allergy Clin Immunol* 2006; 118:S1–15.
23. Cowen MK, Wakefield DB, Cloutier MM. Classifying asthma severity: objective versus subjective measures. *J Asthma* 2007; 44:711–715.
24. Patel P, Philip G, Yang W, Call R, Horak F, LaForce C, Gilles L, Garrett GC, Dass SB, Knorr BA, Reiss TF. Randomized, double-blind, placebo-controlled study of montelukast for treating perennial allergic rhinitis. *Ann Allergy Asthma Immunol* 2005; 95:551–557.
25. Philip G, Malmstrom K, Hampel FC, Weinstein SF, LaForce CF, Ratner PH, Malice MP, Reiss TF. Montelukast for treating seasonal allergic rhinitis: a randomized, double-blind, placebo-controlled trial performed in the spring. *Clin Exp Allergy* 2002; 32:1020–1028.
26. Philip G, Nayak AS, Berger WE, Leynadier F, Vrijens F, Dass SB, Reiss TF. The effect of montelukast on rhinitis symptoms in patients with asthma and seasonal allergic rhinitis. *Curr Med Res Opin* 2004; 20:1549–1558.
27. Philip G, Williams-Herman D, Patel P, Weinstein SF, Alon A, Gilles L, Tozzi CA, Dass SB, Reiss TF. Efficacy of montelukast for treating perennial allergic rhinitis. *Allergy Asthma Proc* 2007; 28:296–304.
28. van Adelsberg J, Philip G, LaForce CF, Weinstein SF, Menten J, Malice MP, Reiss TF. Randomized controlled trial evaluating the clinical benefit of montelukast for treating spring seasonal allergic rhinitis. *Ann Allergy Asthma Immunol* 2003; 90:214–222.
29. van Adelsberg J, Philip G, Pedinoff AJ, Meltzer EO, Ratner PH, Menten J, Reiss TF. Montelukast improves symptoms of seasonal allergic rhinitis over a 4-week treatment period. *Allergy* 2003; 58:1268–1276.
30. Zeiger RS, Bird SR, Kaplan MS, Schatz M, Pearlman DS, Orav EJ, Hustad CM, Edelman JM. Short-term and long-term asthma control in patients with mild persistent asthma receiving montelukast or fluticasone: a randomized controlled trial. *Am J Med* 2005; 118:649–657.