
A randomized, placebo-controlled study of intravenous montelukast in children with acute asthma

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Background: Up to 30% of patients require hospitalization for acute asthma despite standard therapy in the emergency department. In adults, intravenous montelukast added to standard therapy significantly improved forced expiratory volume in 1 second (FEV₁) and reduced hospital admissions compared with standard therapy alone.

Objective: To evaluate the efficacy of intravenous montelukast added to standard therapy in children with acute asthma.

Methods: This was a randomized, double-blind, placebo-controlled, multicenter study of children aged 6 to 14 years conducted from August 25, 2005 to March 17, 2008. Patients with an FEV₁ of 75% or less of the predicted value after up to 120 minutes of standard therapy (eg, oxygen, albuterol, inhaled anticholinergics, and systemic oral corticosteroids) were randomized to intravenous montelukast, 5.25 mg (n = 145), or placebo (n = 131) added to standard therapy. The primary end point was the time-weighted average change in FEV₁ during 60 minutes (Δ FEV_{1[0-60 min]}). Secondary end points included the percentage of patients in whom treatment failed (patients who required hospitalization or for whom a decision to discharge was not reached within 2 hours after drug administration) and the change from baseline in modified pulmonary index score after 60 minutes of treatment.

Results: Montelukast was not significantly more effective than placebo for Δ FEV_{1[0-60 min]} when added to standard therapy (0.08 vs 0.07 L; least squares mean, 0.01; 95% confidence interval, -0.06 to 0.08; *P* = .78). No significant differences were found in the percentages of patients in whom treatment failed or the modified pulmonary index score after 60 minutes. Both treatments were well tolerated.

Conclusions: In this study of children with acute asthma, intravenous montelukast was not significantly better than placebo in improving FEV₁, symptoms, or overall hospital course.

Ann Allergy Asthma Immunol. 2010;104:161–171.

INTRODUCTION

The goals of managing acute asthma exacerbations include correcting hypoxemia, reversing airflow obstruction, and reducing the likelihood of recurrent severe airflow obstruction.¹ Current guideline recommendations for managing acute asthma exacerbations in the emergency department (ED) include supplemental oxygen, short-acting β -agonists (SABAs), and, depending on the response to treatment or the severity of the attack, ipratropium and systemic corticoste-

roids.¹ Studies indicate that although most patients respond sufficiently to SABAs to be discharged,² up to 30% require hospitalization. The addition of anticholinergics further reduces the risk of hospital admissions compared with SABAs alone,³ but early corticosteroid use in the ED has not been definitively shown to reduce admissions.^{4,5} Importantly, response to initial treatment in the ED (ie, within 1 hour) is strongly predictive of the eventual decision to discharge or hospitalize.^{6,7} Thus, there is an overall need for additional

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Disclosures: Dr Morris reports she is the inventor or coinventor of several Children's Hospital & Research Center patent applications, including one for a nutritional formula licensed to Nourish Life (PharmaOmega), has served on scientific advisory committees for Merck and IcaGen, received an educational stipend from INO Therapeutics, and has been a consultant for Biomarin, Gilead Sciences Inc, and the Clinical Advisors Independent Consulting Group. Dr Becker has served on advisory boards in Canada for AstraZeneca, GlaxoSmithKline, Merck Frosst, and Novartis. He has received research support from AstraZeneca, GlaxoSmithKline, Merck Frosst, and Nycomed, as well as from the Allergy Gene Environment Network (AllerGen) of the Centres of Excellence, the Canadian Institutes of Health Research, and the Children's Hospital Foundation of Manitoba. He serves on the Science Committee of the Global Initiative for Asthma (GINA) and was a member of the panel to develop the GINA 2009 report on Global Strategy for Asthma Management and Prevention in Children Five Years and Younger. Dr Piñeiro reports relationships with Bayer, Novartis, and Schering-Plough. Drs Massaad, Green, Smugar, and Gurner are employees of Merck & Co Inc, who may potentially own stock and/or hold stock options in the company.

Funding Sources: This study was sponsored by Merck & Co Inc.

Trial Registration: clinicaltrials.gov Identifier: NCT00117338

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doi:10.1016/j.anai.2009.11.065

rapid-acting agents to reduce the incidence of asthma-related hospitalizations.

Montelukast is a leukotriene receptor antagonist with well-established efficacy in chronic asthma in children, as both monotherapy⁸ and adjunctive therapy to inhaled corticosteroids (ICSs),⁹ and has also been shown to be efficacious in acute asthma.¹⁰ A study evaluating the effect of intravenous (IV) montelukast in treating chronic asthma¹¹ showed significant improvement in forced expiratory volume in 1 second (FEV₁) within 15 minutes compared with both placebo and oral montelukast, and 2 studies of IV montelukast in acute asthma in adults^{12,13} showed significant improvement in FEV₁ compared with placebo as quickly as 10 minutes after administration, with continued significant improvement throughout the full 2-hour study period. The purpose of this study was to assess the efficacy of IV montelukast in treating acute asthma in children when added to standard therapy.

METHODS

Patients and Study Design

This study (Merck protocol 301) was a double-blind, randomized, multicenter study conducted from August 25, 2005 to March 17, 2008 at 36 sites in the United States (19), South America (10), India (3), Mexico (3), and Europe (1). Patients were 6 to 14 years of age with a history of asthmatic symptoms on at least 1 occasion within the previous 3 months presenting at the time of randomization with an acute asthma exacerbation. The protocol was approved by local institutional review boards or independent ethics committees, and written informed consent or assent was obtained from patients and their parent or caregiver before participation.

On arrival, patients entered a 60-minute prestudy period (Figure 1), during which they received standard care for

acute asthma,¹ which may have consisted of oxygen, nebulized SABAs (1.25 to 5 mg every 20 minutes), inhaled or nebulized anticholinergics, and/or oral corticosteroids (prednisone, 1 to 2 mg/kg up to 60 mg, or prednisolone, 1 to 2 mg/kg up to 50 mg). After the prestudy period, patients entered period 1, which could last up to an additional 60 minutes. During this time, they continued to receive standard treatment, consented or assented to the study, and were assessed for eligibility. Patients with an FEV₁ of 75% or less of the predicted value and a modified pulmonary index (mPI) score of 5 or higher on 2 occasions entered period 2, in which they were randomized to IV montelukast, 5.25 mg, or matching placebo delivered as a manual bolus for 2 to 5 minutes according to a computer-generated schedule. The 5.25-mg dose of montelukast used in this study was chosen to approximate, on an age-adjusted basis, the dose of IV montelukast (7 mg) that had previously demonstrated evidence of efficacy in adults with acute asthma.^{12,13} During period 2, patients were permitted to continue receiving standard therapy. Period 2 lasted until a decision was made for discharge from the study site, admission to the hospital, or discontinuation from the study.

Exclusion criteria included known or suspected cause of the symptoms other than asthma (eg, pneumonia, cystic fibrosis) and asthma with life-threatening features (eg, imminent respiratory failure, need for intubation). Oral corticosteroids were permitted before site arrival and during the study (1-2 mg/kg). The use of ICSs was allowed before arrival but not during the prestudy period, period 1, or period 2. The use of antileukotrienes was permitted if taken more than 24 hours before arrival. Excluded therapy included long-acting β -agonists, xanthines, heliox, inhaled cromolyn, β -antagonists, and

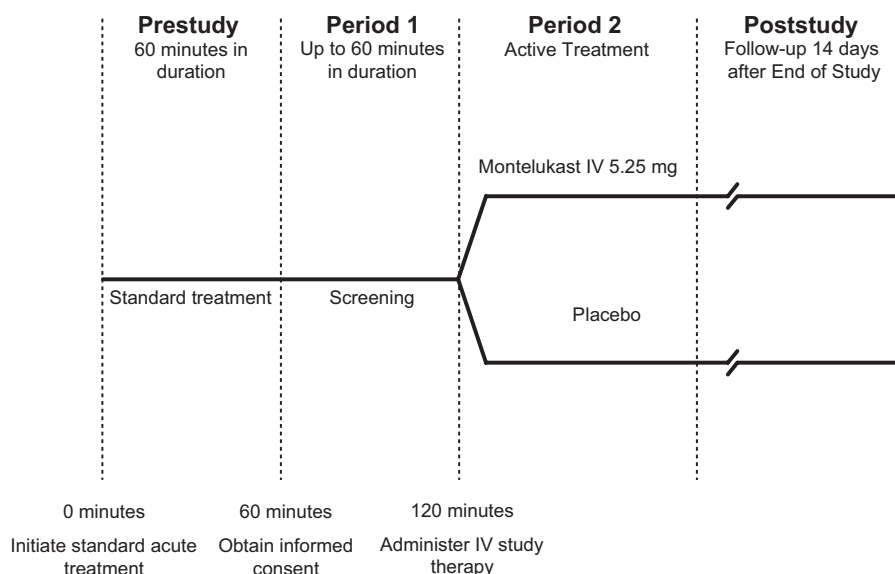


Figure 1. Study diagram. IV indicates intravenous.

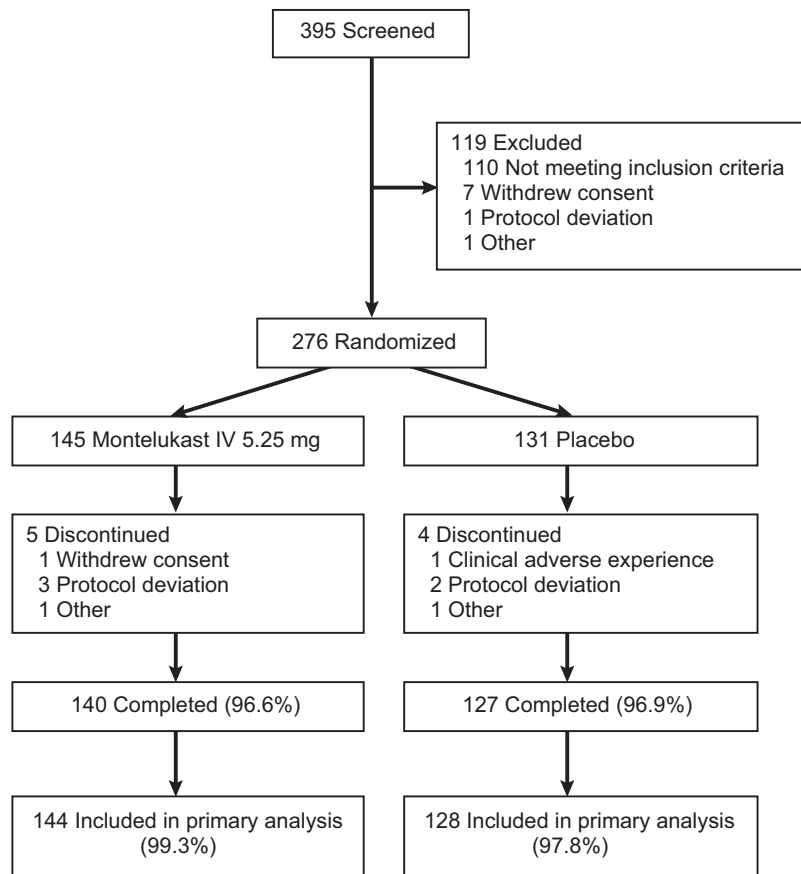


Figure 2. Patient flow through the study. IV indicates intravenous.

long-acting anticholinergics if received less than 24 hours before arrival. Parenteral corticosteroids were not permitted before study site admission or during the study period unless approved in advance by the clinical monitor.

Numbered vials were used to implement allocation. All study personnel, including investigators, study site personnel, patients, monitors, and central laboratory personnel, remained masked to treatment allocation throughout the study. The code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete.

Efficacy and Safety Evaluations

Spirometry was performed at 15, 30, 45, 60, and 120 minutes after drug administration. The primary efficacy end point was the time-weighted average change in FEV₁ from preallocation baseline (period 1) during the first 60 minutes after drug administration (average $\Delta\text{FEV}_{1[0-60 \text{ min}]}$). Key secondary end points included the percentage of patients in whom treatment failed, defined as (1) patients who required hospitalization or (2) patients for whom a decision to discharge had not been reached by 2 hours after drug administration, and the change from baseline in mPI score after 60 minutes of treatment. The mPI¹⁴ score was based on 4 attributes: respiratory rate, wheezing, inspiratory-expiratory ratio, and accessory muscle

use, each scored on a worsening scale of 0 to 3. Individual attribute scores were summed for a total score of 0 to 12. End points for onset of action were also assessed as time-weighted average in FEV₁ during 45 minutes (average $\Delta\text{FEV}_{1[0-45 \text{ min}]}$), the average change in FEV₁ during 30 minutes (average $\Delta\text{FEV}_{1[0-30 \text{ min}]}$), and the change in FEV₁ after 15 minutes. Additional end points included the time-weighted average change in FEV₁ during 2 hours (average $\Delta\text{FEV}_{1[0-2 \text{ hours}]}$), total dose of β -agonist within 2 hours of drug administration, time to decision for hospitalization or discharge, and the change from baseline in oxygen saturation after 2 hours of treatment. Safety and tolerability were assessed by clinical evaluations and adverse experience monitoring.

Statistical Analysis

The primary efficacy analysis was based on the full analysis set population, which included all randomized patients who received double-blind study drug with efficacy measurements at both baseline and at least 1 point during the treatment period. For continuous end points that involved change from baseline (ie, end points derived from FEV₁ measures, mPI score, oxygen saturation), the full analysis set population included all randomized patients who received double-blind study drug and with efficacy measurements both at baseline

Table 1. Baseline Patient Demographics and Characteristics^a

Characteristics	Intravenous montelukast, 5.25 mg (n = 145)	Placebo (n = 131)
Age, mean (SD), y	9.2 (2.4)	8.9 (2.3)
Age, y		
<9	60 (41.4)	63 (48.1)
≥9-<12	57 (39.3)	49 (37.4)
≥12	28 (19.3)	19 (14.5)
Sex		
Male	90 (62.1)	81 (61.8)
Female	55 (37.9)	50 (38.2)
Race		
White (non-Hispanic)	16 (11.0)	16 (12.2)
Black	18 (12.4)	16 (12.2)
Hispanic	59 (40.7)	53 (40.5)
Asian	18 (12.4)	18 (13.7)
Multiracial	34 (23.4)	27 (20.6)
Native American	0 (0.0)	1 (0.8)
Region		
United States	36 (24.8)	39 (29.8)
Europe	8 (5.5)	8 (6.1)
Asia	17 (11.7)	18 (13.7)
Other ^b	84 (57.9)	66 (50.4)
Duration of asthma, mean (SD), y	5.5 (3.1)	4.9 (3.1)
Allergic rhinitis	78 (53.8)	62 (47.3)
FEV ₁ , mean (SD), L	1.1 (0.5)	1.0 (0.5)
FEV ₁ , mean (SD), % predicted	51.8 (16.8)	50.6 (17.4)
Respiratory rate, mean (SD), /min	35.6 (8.0)	35.1 (8.4)
Oxygen saturation, mean (SD), %	92.0 (4.2)	92.2 (4.1)
Prior use of systemic corticosteroids or leukotriene receptor antagonist	6 (4.1)	4 (3.1)
Asthma symptom frequency in the past year		
All year long with or without seasonal flares	66 (45.5)	46 (35.1)
Only during certain seasons	74 (51.0)	81 (61.8)
Asthma symptom frequency in the past month		
Never	34 (23.4)	31 (23.7)
≤2 Times per week	61 (42.1)	57 (43.5)
>2 Times per week	36 (24.8)	33 (25.2)
Continuously	4 (2.8)	1 (0.8)
Every day	7 (4.8)	5 (3.8)
Impact of asthma on work or school in the past year	112 (77.2)	86 (65.6)
ED visits due to asthma in the past year, mean (SD)	2.1 (2.9)	1.4 (1.6)
mPI score, mean	6.5	6.5
Total β-agonist doses in period 1, mg		
0	0 (0.0)	3 (2.3)
>0-2.5	26 (17.9)	30 (22.9)
>2.5-5	34 (23.4)	35 (26.7)
>5	85 (58.6)	63 (48.1)
Time between first drug administration in study center and study drug administration, min		
<60	0 (0.0)	1 (0.8)
60-90	15 (10.3)	9 (6.9)
90-120	82 (56.6)	90 (68.7)
>120	48 (33.1)	31 (23.7)

Abbreviations: ED, emergency department; FEV₁, forced expiratory volume in 1 second; mPI, modified pulmonary index.

^a Data are presented as number (percentage) of patients unless otherwise indicated.

^b South America and Lithuania.

and at least one point during the interval considered. At least 1 postrandomization measurement obtained subsequent to at least 1 dose of study treatment was required for inclusion in the analysis of other end points, including treatment failure

and β-agonist use. Baseline FEV₁ measurement was also required for analyses of these additional end points because a term for baseline FEV₁ (as an indicator of baseline severity) was included in the statistical models.

Table 2. Change in FEV₁ From Baseline (Full Analysis Set Population)^a

FEV ₁ measure	Intravenous montelukast, 5.25 mg (n = 145)	Placebo (n = 131)	Difference between montelukast and placebo (95% CI)	P value
Time-weighted average Δ FEV ₁ [0-60 min] (primary end point)	0.08	0.07	0.01 (−0.06 to 0.08)	.78
Time-weighted average Δ FEV ₁ [0-45 min]	0.07	0.05	0.02 (−0.05 to 0.09)	.61
Average Δ FEV ₁ [0-30 min]	0.06	0.05	0.01 (−0.06 to 0.08)	.77
Average Δ FEV ₁ [0-15 min]	0.06	0.01	0.04 (−0.02 to 0.11)	.17
Time-weighted average Δ FEV ₁ [0-2 hours]	0.10	0.08	0.02 (−0.06 to 0.09)	.68

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; Δ FEV₁, time-weighted average change in FEV₁.

^a All values are expressed as least squares mean change from baseline.

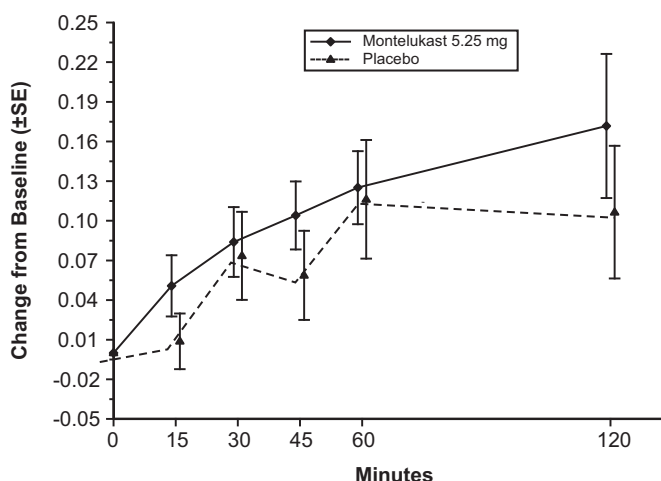


Figure 3. Change from baseline in forced expiratory volume in 1 second during 2 hours (full analysis set population). Data are expressed as mean $\pm$ SE.

The primary end point was analyzed using an analysis of covariance (ANCOVA) model using baseline FEV₁ as a covariate and included factors for treatment and region (United States, non-United States). To calculate the primary end point of average Δ FEV₁[0-60 min], each interval between any measurement and the measurement before it was used as the weighting factor (eg, the weights for the measurements at 15, 30, 45, and 60 minutes are 1/4, 1/4, 1/4, and 1/4, respectively). The change from baseline in mPI score was analyzed using an ANCOVA model similar to the one described for the primary end point, using the baseline mPI score as a covariate. The percentage of patients in whom treatment failed was compared using a logistic regression model with factors for treatment and baseline FEV₁. The times to decision for hospitalization or for discharge to home were analyzed using a Cox regression model with factors for treatment and baseline FEV₁. β -Agonist use was compared using a nonparametric ANOVA model on normalized (Tukey) scores, and change in oxygen saturation was analyzed using the same ANCOVA model as described herein for the change from baseline in mPI score but using the baseline oxygen saturation as a covariate.

To determine the onset of action of IV montelukast compared with placebo, a prespecified step-down procedure was used to adjust for multiplicity: if the primary efficacy end point was significant at the .05 level, then the 2 treatments would be compared to assess the effect on FEV₁ for 45 minutes, 30 minutes, and 15 minutes (in that order, with each step requiring significance at the .05 level). Because the secondary end points were supportive in nature, no multiplicity adjustment was performed for their assessments.

Prespecified subgroup analyses of the primary and secondary variables were performed for age (by tertiles), race, baseline FEV₁ (less than or equal to vs greater than the median), baseline mPI score (less than or equal to vs greater than the median), pulse oximetry (less than or equal to vs greater than the median), and prior systemic corticosteroid and/or antileukotriene use (yes/no). In addition, supportive analyses of the major end points were performed using a “per protocol” population that excluded patients who had significant protocol violations during the trial. The criteria for exclusion from the per-protocol population were established after the study started but before unmasking and database lock. A sample of 130 patients per treatment group would provide 90% power at $\alpha = .05$ to detect a treatment effect size (treatment difference/standard deviation) of 0.40 for the time-weighted average Δ FEV₁[0-60 min].

RESULTS

Patients

A total of 276 patients were randomized: 145 to montelukast and 131 to placebo (Figure 2). Approximately 98% of all patients completed the study, with protocol deviation being the most common reason for discontinuation. Baseline patient demographics and asthma variables are given in Table 1. Most patients were male (62%) and Hispanic (41%), with a mean (SD) age of 9.1 (2.3) years. There was a somewhat unequal distribution between the 2 treatment groups for age tertile, study region, history of allergic rhinitis, asthma symptom frequency, impact of asthma on school or work, β -agonist doses in period 1, and time between first drug administration and study drug administration. Baseline factors were otherwise similar between the groups.

Table 3. Secondary Efficacy Outcomes (Full Analysis Set Population)

Outcome	Intravenous montelukast, 5.25 mg (n = 145)	Placebo (n = 131)	Difference between montelukast and placebo (95% CI)	P value
mPI change from baseline at 60 minutes after study drug administration, LS mean	−2.95	−2.96	0.02 (−0.41 to 0.45)	.93
Total doses of β -agonist within 2 hours after study medication administration, median	1.0	0.6	0.00 (0.00 to 0.00) ^{a,b}	.58
Oxygen saturation change from baseline at 120 minutes after study medication administration, LS mean	2.69	2.52	0.18 (−0.44 to 0.79)	.57

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; LS, least squares; mPI, modified pulmonary index.

^a Difference of medians computed by Hodges-Lehmann estimation.

^b Distribution-free CI based on rank sum test.

Efficacy

For the primary efficacy end point based on the full analysis set population, the least squares mean time-weighted average Δ FEV_{1[0-60 min]} was 0.08 L for patients receiving IV montelukast, 5.25 mg, and 0.07 L for patients receiving placebo; the difference was not statistically significant (0.01; 95% confidence interval [CI], −0.06 to 0.08; $P = .78$) (Table 2). The per-protocol analysis was similar (treatment difference, 0.03; 95% CI, −0.06 to 0.11; $P = .54$). The overall changes in FEV₁ during 2 hours are shown in Figure 3. No significant or clinically meaningful differences in the primary end point and no significant treatment-by-subgroup interactions were found for the prespecified subgroups (data not shown).

No statistically significant differences were found between treatment groups for the secondary end points of onset of action (Table 2), change from baseline in mPI score, total dose of β -agonist use (Table 3), percentage of patients in whom treatment failed, or individual measure of treatment failure (ie, time to discharge home or time to hospitalization) (Figure 4). Analysis of change in mPI score from baseline by race showed significantly less improvement in blacks receiving montelukast (−2.5) than placebo (−4.1; treatment difference, 1.62; 95% CI, 0.39 to 2.85). No other significant differences were found by race for mPI score. In addition, the odds of treatment failure were higher in black patients with montelukast (odds ratio [OR], 4.7; 95% CI, 0.97 to 22.7) than other races (white, 0.00; Hispanic, 1.00; and Asian/other, 0.89).

Post Hoc Efficacy Analyses

Because of the differences in total β -agonist use in period 1 (more use of >5 mg in the montelukast group), frequency of asthma symptoms (more patients with year-round asthma in the montelukast group), and impact of asthma on work or school (more frequent in the montelukast group) that might indicate that the patients randomized to montelukast had more severe asthma, we conducted several post hoc analyses of the primary and key secondary variables to assess whether outcome was affected by asthma severity (Table 4). For the primary end point of Δ FEV_{1[0-60 min]}, there was a trend toward improved efficacy

compared with placebo in all 3 of the “lower severity” subgroups (ie, ≤ 5 mg of total β -agonists in period 1, seasonal asthma only, and no impact of asthma on school or work). For change in mPI score from baseline and treatment failure, the results were inconsistent and did not alter the main conclusions of the study.

Safety and Tolerability

No statistically significant differences were found between treatment groups for clinical adverse events (Table 5). There were 2 serious adverse events in each treatment group, none of which was considered to be drug related: 3 patients had worsening asthma (2 in the montelukast group, 1 patient in the placebo group), and 1 patient in the placebo group received an overdose of study medication. No patients in the montelukast group discontinued treatment because of an adverse event. The most common adverse events were respiratory disorders (4.8% montelukast vs 7.0% placebo), gastrointestinal disorders (3.4% montelukast vs 4.6% placebo), and nervous system disorders (4.2% montelukast vs 1.6% placebo).

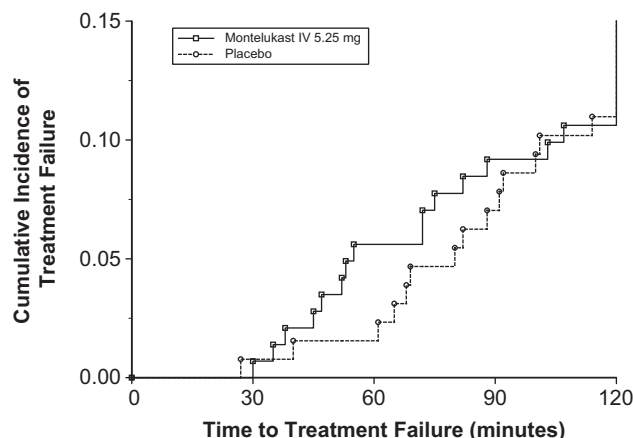
DISCUSSION

The purpose of this study was to evaluate the efficacy, safety, and tolerability of IV montelukast in acute asthma when added to standard therapy in children aged 6 to 14 years. We found no significant differences between montelukast and placebo for any efficacy end point, including the primary efficacy end point of average Δ FEV_{1[0-60 min]}. These results stand in contrast to those from earlier studies of IV montelukast in adults.

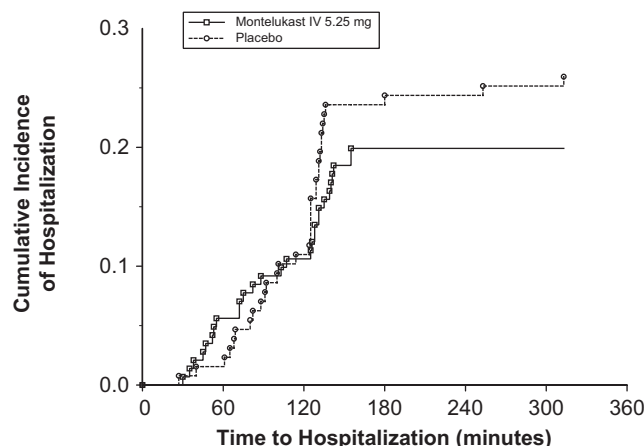
In a study involving 3 US sites, Dockhorn and colleagues¹¹ compared IV montelukast, 7 mg, oral montelukast, 10 mg, and placebo in a 24-hour study (N = 51) of adults with chronic asthma who had an FEV₁ of 40 or more and 80% or less of the predicted value in which the use of only ICSs (in up to 25% of patients) and albuterol was permitted. Compared with placebo, IV montelukast caused a significant improvement in FEV₁ expressed as area under the curve for 24 hours (21% vs 8%, $P < .001$) and the percentage change in FEV₁ from baseline beginning at 15 minutes after dosing

($P < .001$). The benefit of montelukast was preserved for at least 24 hours, suggesting that a single injection of IV montelukast could be a highly effective treatment for acute asthma.

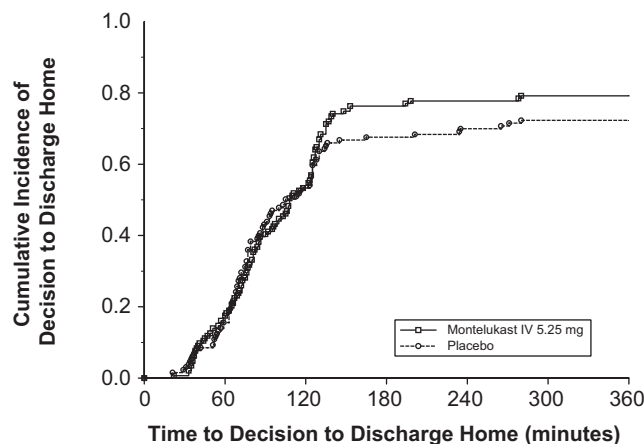
A. Cumulative incidence of all treatment failures



B. Cumulative incidence of hospitalization



C. Cumulative incidence discharge home



Camargo and colleagues¹² conducted a larger study ($N = 201$) at 16 sites within the United States comparing IV montelukast, 7 mg, IV montelukast, 14 mg, and placebo in adults with acute asthma. After a 60-minute screening period during which patients received oxygen and albuterol, those requiring additional therapy ($FEV_1 < 70\%$ predicted) were randomized to IV montelukast or placebo added to oxygen and as-needed nebulized albuterol, 2.5 mg. Corticosteroids (oral prednisone, 60 mg) were allowed beginning 20 minutes after masked study therapy. They found both doses of IV montelukast to be superior to placebo as measured by the primary end point of $FEV_{1[0-20 \text{ min}]}$ ($P = .007$ for both active groups pooled), with significant differences observed as early as 10 minutes after dosing ($P = .03$) and continuing during the 2 hours studied ($P = .003$). No difference was found between montelukast and placebo in the number of patients in whom treatment failed (defined as hospitalization, prolonged short-term treatment [>6 hours], or need for excluded medication). However, after adjusting for a significant ($P < .001$) interaction with baseline FEV_1 , the benefit in favor of montelukast was significant ($P < .05$) for this end point as well. In addition, patients receiving montelukast required significantly fewer oral corticosteroids ($P < .05$), and significantly fewer patients in the montelukast groups required more than 2 β -agonist doses after study drug administration ($P < .05$).

Most recently, a large ($N = 583$), multinational (34 US sites and 28 sites in 15 other countries) study was conducted in adults comparing IV montelukast, 7 mg, and placebo.¹³ After a 60-minute screening period during which time patients received oxygen and albuterol, patients with FEV_1 of 50% or less of the predicted value were randomized to IV montelukast or placebo added to standard therapy of oxygen, albuterol, and inhaled ipratropium every 60 minutes as needed. All patients received systemic oral corticosteroids (prednisone, 60 mg, or prednisolone, 50 mg) immediately after study drug administration. The IV montelukast was significantly better than placebo for the primary end point of average $\Delta FEV_{1[0-60 \text{ min}]}$ (0.3 vs 0.22 L, $P \leq .001$). The benefit of IV montelukast was seen as early as 10 minutes, the earliest time point assessed (ΔFEV_1 at 10 minutes, $P = .008$). No differences were found for treatment failure (OR, 0.92; 95% CI, 0.63 to 1.34; $P = .65$) or β -agonist use between the groups.

Overall, these 3 previous studies showed unequivocally significant improvements in FEV_1 with IV montelukast compared with placebo that began as early 10 minutes and were sustained for as long as 24 hours when the drug was admin-

Figure 4. Treatment failures (full analysis set population). A, Cumulative incidence of all treatment failures. Kaplan-Meier estimates of treatment failure. The hazard ratio (HR) for intravenous (IV) montelukast, 5.25 mg, compared with placebo was 1.03 (95% confidence interval [CI], 0.73 to 1.48) ($P = .85$). B, Cumulative incidence of hospitalization HR was 0.81 (95% CI, 0.49 to 1.35) ($P = .42$). C, Cumulative incidence of decision to discharge HR was 1.13 (95% CI, 0.85 to 1.48) ($P = .40$).

Table 4. Post Hoc Efficacy Analyses as a Function of Baseline Markers of Asthma Severity (Full Analysis Set Population)

Subgroup	Total β -agonist doses in period 1, mg	
	>5 mg	$\leq$ 5 mg
Δ FEV ₁ [0-60 min]		
Intravenous montelukast, 5.25 mg		
Total No. of patients	84	60
LS mean (95% CI)	0.08 (0.02 to 0.14)	0.09 (0.01 to 0.17)
Placebo		
Total No. of patients	60	68
LS mean (95% CI)	0.08 (0.01 to 0.16)	0.06 (−0.01 to 0.13)
Treatment effect, LS mean (95% CI) ^a	−0.01 (−0.10 to 0.09)	0.03 (−0.08 to 0.13)
Change from baseline in mPI score		
Intravenous montelukast, 5.25 mg		
Total No. of patients	84	59
LS mean (95% CI)	−2.58 (−2.96 to −2.20)	−3.5 (−3.95 to −3.05)
Placebo		
Total No. of patients	60	68
LS mean (95% CI)	−2.81 (−3.25 to −2.36)	−3.12 (−3.55 to −2.70)
Treatment effect, LS mean (95% CI) ^a	0.23 (−0.36 to 0.81)	−0.38 (−1.00 to 0.24)
Treatment failure		
Intravenous montelukast, 5.25 mg		
Total No. of patients	85	60
No. (%) of patients [95% CI]	41 (48.2) [37.26 to 59.34]	24 (40) [27.56 to 53.46]
Placebo		
Total No. of patients	63	68
No. (%) of patients [95% CI]	35 (55.6) [42.49 to 68.08]	24 (35.3) [24.08 to 47.83]
Treatment effect OR (95% CI) ^a	0.71 (0.36 to 1.39)	1.25 (0.61 to 2.57)

Abbreviations: CI, confidence interval; Δ FEV₁[0-60 min], time-weighted average change in forced expiratory volume in 1 second during 60 minutes; mPI, modified pulmonary index; OR, odds ratio.

^a Intravenous montelukast, 5.25 mg, vs placebo.

istered in patients with chronic asthma¹¹ and when it was added to standard regimens for acute asthma care.^{12,13} Thus, it is unclear why the present study failed to show any benefit over placebo. One possible confounder was a tendency for patients in the montelukast group to have more severe asthma at baseline. Notably, patients in the montelukast group were more likely to have year-round asthma (45.5% vs 35.1%), were less likely to have only seasonal asthma (51.0% vs 61.8%), and had a higher likelihood of asthma having an impact on school or work (77.2% vs 65.6%), all of which may have introduced bias in the montelukast group against response to treatment. This finding is supported by the observation that despite similar acute asthma presentations (eg, as demonstrated by prandomization FEV₁, respiratory rate, and oxygen saturation), patients receiving montelukast were more likely to receive more than 5 mg of β -agonist in period 1 (58.6% vs 48.1%).

An additional consequence of the difference in period 1 β -agonist use is that it would be difficult to provide additional detectable bronchodilation on top of what was provided by nebulized β -agonist (which was continued during the active treatment). This hypothesis is at least partially supported by our post hoc analyses, which show larger differences in FEV₁

and mPI scores from placebo in the group that received 5 mg or less of β -agonist than in the group that received more than 5 mg. This pattern of increased response in the less severe group (ie, $\leq$ 5 mg) was not true for patients in whom treatment had failed; the OR favored montelukast in the more than 5-mg group (OR, 0.71) but favored the placebo group in the 5-mg or less group (OR, 1.25). Interestingly, however, the actual percentage of treatment failures with montelukast was lower in the 5-mg or less group (40.0%) than in the more than 5-mg group (48.2%), which may further suggest increased response in the lower severity group.

Patients in the montelukast group may have received a greater amount of standard therapy overall, including inhaled anticholinergic therapy in addition to the aforementioned β -agonist therapy, which might make detection of response to montelukast less likely. It is also possible that the differences in prandomization β -agonist use and time in study center may reflect differences in ED practices and not a difference in severity, although the discrepancy might still have influenced the results.

Substantial differences were also found in study designs between the 3 adult trials and the current trial, which may have affected our results. In the study by Dockhorn et al¹¹

Frequency of presence of asthma symptoms in past year		Impact of asthma on work or school in the past year	
All year with or without seasonal	Only during certain seasons or none	Yes	No
65 0.07 (0.00 to 0.15)	77 0.09 (0.03 to 0.16)	112 0.08 (0.03 to 0.14)	30 0.09 (−0.02 to 0.20)
46 0.08 (−0.01 to 0.17) −0.01 (−0.12 to 0.11)	80 0.07 (0.01 to 0.14) 0.02 (−0.07 to 0.12)	86 0.11 (0.04 to 0.17) −0.02 (−0.11 to 0.06)	40 0.01 (−0.09 to 0.10) 0.09 (−0.06 to 0.23)
65 −3.01 (−3.45 to −2.57)	76 −2.96 (−3.37 to −2.56)	112 −3.08 (−3.42 to −2.75)	29 −2.6 (−3.25 to −1.95)
45 −2.9 (−3.43 to −2.38) −0.11 (−0.79 to 0.58)	81 −3.07 (−3.46 to −2.67) 0.1 (−0.46 to 0.67)	85 −2.94 (−3.32 to −2.56) −0.14 (−0.65 to 0.36)	41 −3.15 (−3.70 to −2.60) 0.55 (−0.31 to 1.40)
66 33 (50) [37.43 to 62.57]	77 32 (41.6) [30.43 to 53.36]	112 49 (43.8) [34.39 to 53.44]	31 16 (51.6) [33.06 to 69.85]
46 24 (52.2) [36.95 to 67.11] 1.04 (0.48 to 2.24)	81 33 (40.7) [29.95 to 52.23] 1.01 (0.53 to 1.91)	86 37 (43) [32.39 to 54.15] 1.08 (0.61 to 1.91)	41 20 (48.8) [32.88 to 64.87] 1.13 (0.44 to 2.93)

of adults with chronic stable asthma, there was no pranandomization treatment period during which patients received additional medication. In the 2 more recent studies in acute asthma, there was a fixed 60-minute pranandomization period during which patients received only oxygen and albuterol.^{12,13} In the present study, patients had 2 pranandomization periods of up to 120 minutes' total duration during which they received full standard therapy. This increased time and more aggressive treatment before randomization might have made it more difficult to show a benefit with montelukast, particularly given that the on-treatment study period was only 120 minutes. It is possible that the combination of an extra 60-minute prestudy period, aggressive pretreatment, and increased β -agonist use in the montelukast group together affected the ability to detect a treatment difference during the relatively short postrandomization period specified in the protocol. Indeed, both the change in FEV₁ over time (Figure 3) and the Kaplan-Meier curves for treatment failures (Figure 4B and C) suggest a distinct separation between treatment groups favoring montelukast after 120 minutes.

Despite these observations, we cannot exclude the possibility that IV montelukast simply was not efficacious in this

pediatric population. It is unlikely that lack of benefit attributable to montelukast is attributable to an overly robust response in the placebo (standard care) group, which has been well described in asthma.¹⁵⁻¹⁷ The changes at 60 minutes in the placebo groups ranged from 5% to 24% in the previous IV montelukast studies, but the change was 8% in the present study.

As noted, black patients receiving montelukast had less improvement in mPI scores and had higher odds of treatment failure. Although this observation could have been simply due to chance, the findings of worse asthma outcomes in blacks has been observed in other studies of asthma.^{18,19} African American ethnicity is a risk factor for asthma severity, with higher rates of hospitalization and mortality compared with white children.^{20,21} It is possible that unquantifiable socioeconomic factors may have confounded our results in this regard. Moreover, mPI assessment is a subjective measure. Specifically, measuring respiratory rate and inspiratory-expiratory ratio and identifying wheezing and accessory muscle use are all prone to individual interpretation. Thus, by the one purely objective measure of response in this study—FEV₁—no significant difference by race was found.

Table 5. Clinical Adverse Experiences^a

Adverse experience	Intravenous montelukast, 5.25 mg, No. (%) (n = 145)	Placebo, No. (%) (n = 131)
Clinical adverse experience	22 (15.2)	21 (16.0)
Drug-related adverse experience ^b	2 (1.4)	3 (2.3)
Serious adverse experience	2 (1.4)	2 (1.5)
Discontinued treatment because of adverse experience	0 (0.0)	1 (0.8)

^a Although a patient may have 2 or more adverse experiences, the patient is counted only once in a category or overall.

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

Irrespective of the reasons for the results in our study, the outcome reinforces the need for caution in extrapolating results from adult studies to pediatric use. Even within the pediatric age range, differences in efficacy by age can be significant,^{22,23} perhaps underscoring the more variable nature of asthma in children.²⁴ Importantly, in this multicenter, multinational trial of acute asthma, both ED- and patient-dependent factors may influence treatment decisions. Disposition decisions are often physician dependent and can be affected by clinically independent, patient-defined elements, such as time of arrival in the ED, ED volume, age of patient, availability of assistance at home, access to transportation, insurance status, and a timely ability to obtain asthma medication, patient ability to follow up, cultural expectations, and need for disease-related education.^{19,25-28} In addition, there are institutional determinants, such as degree of bed use, ED flow, and need for discharge preparation.^{19,25-29} Overall, then, it is unlikely that criteria for discharge or hospital admission of asthma patients will be uniform across medical centers and regions, even when clinical standards are putatively consistent. This inevitable variability in practice makes it difficult to establish a universally applicable clinical outcome measure.

In addition, to allow for individualized treatment based on severity, standard care in this study did not consist of strict administration instructions but rather general guidelines of allowed and excluded therapies. Therefore, it was up to the individual investigator's discretion how to administer allowed therapy, which may not have been consistent across sites for a given level of asthma severity. Although a post hoc analysis of outcomes by study center might support this possibility, the large number of very small study sites limits the usefulness of such analyses. Thus, despite the uniformity of the efficacy results in the present study, we cannot exclude intersite treatment differences as a possible reason for the outcomes in this trial.

In conclusion, in this study IV montelukast added to standard therapy for acute asthma care in children did not significantly improve lung function, symptoms, or overall hospital course compared with standard therapy alone. There were numerous and substantial baseline differences between groups that may have confounded the results. During the trial, IV montelukast was well tolerated, and no specific safety concerns were raised. Acute asthma in children remains a significant unmet medical need; further studies are necessary to identify appropriate interventions in this population.

ACKNOWLEDGMENTS

We thank Elizabeth Beckford-Brathwaite and Otis Johnson of Merck Research Laboratories for their contributions to the conduct of the study and Jennifer Pawlowski of Merck Research Laboratories for her assistance with the preparation of the manuscript.

REFERENCES

1. National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma: Full Report 2007*. Bethesda, MD: National Institutes of Health; 2007.
2. Hejal R, Galan G, Dixon L, McFadden ER Jr. Observations on the effects of aerosolized albuterol in acute asthma. *Am J Respir Crit Care Med*. 1997;155:454-458.
3. Rodrigo GJ, Castro-Rodriguez JA. Anticholinergics in the treatment of children and adults with acute asthma: a systematic review with meta-analysis. *Thorax*. 2005;60:740-746.
4. Rowe BH, Spooner C, Ducharme FM, Bretzlaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev*. 2001;CD002178.
5. Rodrigo G, Rodrigo C. Corticosteroids in the emergency department therapy of acute adult asthma: an evidence-based evaluation. *Chest*. 1999;116:285-295.
6. Rodrigo G, Rodrigo C. Early prediction of poor response in acute asthma patients in the emergency department. *Chest*. 1998;114:1016-1021.
7. Kelly AM, Kerr D, Powell C. Is severity assessment after one hour of treatment better for predicting the need for admission in acute asthma? *Respir Med*. 2004;98:777-781.
8. Knorr B, Matz J, Bernstein JA, et al; Pediatric Montelukast Study Group. Montelukast for chronic asthma in 6- to 14-year-old children: a randomized, double-blind trial. *JAMA*. 1998; 279:1181-1186.
9. Simons FE, Villa JR, Lee BW, et al. Montelukast added to budesonide in children with persistent asthma: a randomized, double-blind, crossover study. *J Pediatr*. 2001;138:694-698.
10. Harmanci K, Bakirtas A, Turktas I, Degim T. Oral montelukast treatment of preschool-aged children with acute asthma. *Ann Allergy Asthma Immunol*. 2006;96:731-735.
11. Dockhorn RJ, Baumgartner RA, Leff JA, et al. Comparison of the effects of intravenous and oral montelukast on airway function: a double blind, placebo controlled, three period, crossover study in asthmatic patients. *Thorax*. 2000;55:260-265.
12. Camargo CA Jr, Smithline HA, Malice MP, Green SA, Reiss TF. A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med*. 2003;167:528-533.
13. A Multicenter, Randomized, Double-Blind Study Comparing the Clinical Effects of Intravenous Montelukast With Placebo in Patients With Acute Asthma. ClinicalStudyResults.org. Accessed February 17, 2009.
14. Nelsen LM, Norquist JM, Zhu X, Gurner DM, Gorelick MH. Measuring severity of acute asthma in pediatric patients. *J Allergy Clin Immunol*. 2008;121:S80.
15. 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.

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16. 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.
 17. 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.
 18. Weber EJ, Silverman RA, Callahan ML, et al. A prospective multi-center study of factors associated with hospital admission among adults with acute asthma. *Am J Med*. 2002;113:371–378.
 19. Markoff BA, MacMillan JF Jr, Kumra V. Discharge of the asthmatic patient. *Clin Rev Allergy Immunol*. 2001;20:341–355.
 20. Lin RY, Pitt TJ, Lou WY, Yi Q. Asthma hospitalization patterns in young children relating to admission age, infection presence, sex, and race. *Ann Allergy Asthma Immunol*. 2007;98:139–145.
 21. Castro M, Schechtman KB, Halstead J, Bloomberg G. Risk factors for asthma morbidity and mortality in a large metropolitan city. *J Asthma*. 2001;38:625–635.
 22. Szeffler SJ, Phillips BR, Martinez FD, et al. Characterization of within-subject responses to fluticasone and montelukast in childhood asthma. *J Allergy Clin Immunol*. 2005;115:233–242.
 23. Johnston NW, Mandhane PJ, Dai J, et al. Attenuation of the September epidemic of asthma exacerbations in children: a randomized, controlled trial of montelukast added to usual therapy. *Pediatrics*. 2007;120:e702–e712.
 24. Chipps BE, Spahn JD, Sorkness CA, et al. Variability in asthma severity in pediatric subjects with asthma previously receiving short-acting beta₂-agonists. *J Pediatr*. 2006;148:517–521.
 25. Stewart M, Werneke U, MacFaul R, Taylor-Meek J, Smith HE, Smith IJ. Medical and social factors associated with the admission and discharge of acutely ill children. *Arch Dis Child*. 1998;79:219–224.
 26. Henry RL. Outcome evaluation of early discharge after hospitalization for asthma. *Curr Opin Allergy Clin Immunol*. 2006;6:172–174.
 27. Kleinman A, Eisenberg L, Good B. Cure, illness, and care: clinical lessons from anthropologic and cross-cultural research. *Ann Intern Med*. 1978;88:251–258.
 28. Jackson P. The impact of health insurance status on emergency room services. *J Health Soc Policy*. 2001;14:61–74.
 29. Blanchard JC, Haywood YC, Scott C. Special contributions: racial and ethnic disparities in health: an emergency medicine perspective. *Acad Emerg Med*. 2003;10:1289–1293.
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