

A randomized placebo-controlled study of intravenous montelukast for the treatment of acute asthma

Carlos A. Camargo, Jr, MD, DrPH,^a Deborah M. Gurner, MD, PhD,^b Howard A. Smithline, MD, MS,^c Rocio Chapela, MD,^d Leonardo M. Fabbri, MD,^e Stuart A. Green, MD,^b Marie-Pierre Malice, PhD,^b Catherine Legrand, PhD,^b S. Balachandra Dass, PhD,^b Barbara A. Knorr, MD,^b and Theodore F. Reiss, MD^b *Boston and Springfield, Mass, Rahway, NJ, Mexico City, Mexico, and Modena, Italy*

Background: Current treatments for acute asthma provide inadequate benefit for some patients. Intravenous montelukast may complement existent therapies.

Objective: To evaluate efficacy of intravenous montelukast as adjunctive therapy for acute asthma.

Methods: A total of 583 adults with acute asthma were treated with standard care during a ≤ 60 -minute screening period. Patients with $FEV_1 \leq 50\%$ predicted were randomly allocated to intravenous montelukast 7 mg ($n = 291$) or placebo ($n = 292$) in addition to standard care. This double-blind treatment period lasted until a decision for discharge, hospital admission, or discontinuation from the study. The primary efficacy endpoint was the time-weighted average change in FEV_1 during 60 minutes after drug administration. Secondary endpoints included the time-weighted average change in FEV_1 at various intervals (10-120 minutes) and percentage of patients with treatment failure (defined as hospitalization or lack of decision to discharge by 3 hours postadministration).

Results: Montelukast significantly increased FEV_1 at 60 minutes postdose; the difference between change from baseline for placebo (least-squares mean of 0.22 L; 95% CI, 0.17, 0.27) and montelukast (0.32 L; 95% CI, 0.27, 0.37) was 0.10 L (95% CI, 0.04, 0.16). Similar improvements in FEV_1 -related variables were seen at all time points (all $P < .05$). Although treatment failure did not differ between groups (OR 0.92; 95% CI, 0.63, 1.34), a prespecified subgroup analysis suggests likely benefit for intravenous montelukast at US sites.

Conclusion: Intravenous montelukast added to standard care in adults with acute asthma produced significant relief of airway obstruction throughout the 2 hours after administration, with an onset of action as early as 10 minutes. (*J Allergy Clin Immunol* 2010;125:374-80.)

Key words: Intravenous montelukast, acute asthma, asthma exacerbation, FEV_1 , hospitalization, leukotriene receptor antagonist, randomized trial

Asthma is characterized by exacerbations that may be life-threatening. These exacerbations are induced by triggers such as viruses, aspirin, allergens, and physical exertion that cause the release of inflammatory mediators, including leukotrienes.^{1,2} Although current standard treatments for acute asthma—including supplemental oxygen, β_2 -agonists, corticosteroids, and anticholinergics (for severe exacerbations)—are quite effective in most patients, they are inadequate for rapid and sustained improvement in a significant proportion.³⁻⁵ Therefore, there is a need for new treatment options that provide benefits beyond the current standard treatments.

Kuitert and Watson⁶ recently reviewed the efficacy of adjunctive oral and intravenous leukotriene inhibitors/receptor antagonists in acute asthma and noted the paucity of studies evaluating clinical outcomes with these agents. Montelukast is a potent leukotriene receptor antagonist that, when taken orally, provides benefit in asthma by decreasing airway inflammation and reversing bronchoconstriction.⁷⁻⁹ Coadministration of montelukast with β_2 -agonist bronchodilators or corticosteroids provides added benefit.¹⁰⁻¹² Dockhorn et al¹³ showed that intravenous montelukast improved FEV_1 in patients with chronic asthma, and Camargo et al¹⁴ found that the addition of intravenous montelukast to standard care produced a rapid improvement in FEV_1 in acute asthma. A role for montelukast in acute asthma was supported by the observation of increased urinary leukotriene E_4 levels in patients with acute asthma.¹⁵ Studies of intravenous formulation of other antileukotriene agents, such as intravenous zileuton,¹⁶ remain to be reported.

Asthma guidelines recognize the evaluation of lung function as critical to the management of acute asthma.^{4,17} FEV_1 and peak expiratory flow measurements are objective assessments of the severity of asthma exacerbations and the response of patients to treatment. Indeed, lung function is the single strongest predictor of hospitalization.¹⁸ Rapid and sustained bronchodilation, together with the attenuation of airway inflammation and the prevention of relapse, remain the immediate goals of emergency physicians treating patients with acute asthma.

Thus, the aim of this study was to investigate further the effect of intravenous montelukast in addition to standard therapy in the

From ^athe Department of Emergency Medicine, Massachusetts General Hospital, Harvard Medical School, Boston; ^bMerck Research Laboratories, Rahway; ^cthe Department of Emergency Medicine, Baystate Medical Center, Tufts University School of Medicine, Springfield; ^dInstituto Nacional de Enfermedades Respiratorias, Unidad de Investigación, Clínica de Asma, Mexico City; and ^ethe Department of Respiratory Diseases, University of Modena and Reggio Emilia, Modena.

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Reprint requests: Carlos A. Camargo, Jr, MD, DrPH, Department of Emergency Medicine, Massachusetts General Hospital, 326 Cambridge Street, Suite 410, Boston, MA 02114. E-mail: ccamargo@partners.org.

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Abbreviations used

AE: Adverse experience
LS: Least squares
OR: Odds ratio

treatment of acute asthma. The primary endpoint of the study was change in lung function (FEV_1).

METHODS

Patients and study design

This study was conducted between July 2004 and February 2007 in the United States (34 sites) and 15 other countries (28 sites). Subjects were ≥ 15 years old, had ≥ 1 year history of physician-diagnosed asthma, and presented with an acute exacerbation of asthma. Patients > 54 years were included if they also had documented FEV_1 reversibility $\geq 15\%$ after β_2 -agonist treatment during the current episode or within the past 5 years, or if their lifetime tobacco exposure was ≤ 10 pack-years. Exclusion criteria included clinically significant, active comorbid disease; a body mass index > 35 kg/m²; or a smoking history of > 15 pack-years.

The study was designed to be consistent with the existing standard care for acute asthma. At the time patient recruitment began, the standard of care was most recently described in the 2002 Global Initiative for Asthma recommendations.¹⁹ On arrival, patients received standard treatment during a ≤ 60 -minute screening period (period I): oxygen, inhaled short-acting β_2 -agonist (2.5-5 mg in 3 mL saline every 20 minutes) as needed, and inhaled ipratropium (not to exceed 36 μ g per hour) or nebulized ipratropium (not to exceed 500 μ g per hour) as needed. Patients with $FEV_1 \leq 50\%$ predicted on all measurements were allocated (1:1) to double-blind therapy (according to a computer-generated randomization schedule with a blocking factor of 4 provided by the study sponsor) during the active treatment period (period II), which began with the intravenous administration (manual bolus over 2-5 minutes) of either placebo or montelukast 7 mg; allocation and administration of study drug had to occur within 60 minutes of initiation of the standard treatment. Study drug (light-protected lyophilized product reconstituted in 20 mL 3.3% dextrose/0.3% sodium chloride [supplied together with the study drug]) was prepared in a foil-wrapped syringe (to ensure adequate blinding) by a qualified person who was not directly associated with the care of the patients; the intravenous line was flushed with 5 mL diluent before and after administration of study drug. Investigators were instructed to administer systemic corticosteroids (60 mg prednisone or 50 mg prednisolone orally) immediately after infusion of study drug. All patients continued to receive standard treatment in period II, consisting of oxygen therapy, β_2 -agonist every 20 minutes as needed, and ipratropium every 60 minutes as needed. Period II lasted until a decision was made for discharge from the study site, admission to the hospital, or discontinuation from the study. A follow-up telephone interview was conducted approximately 14 days after the patient completed period II.

Parenteral corticosteroids or antileukotriene agents were not permitted within 12 hours of initial presentation or during period I; oral corticosteroids and antileukotriene agents were not allowed during period I. Additional medications were not permitted during periods I and II, including inhaled corticosteroids, long-acting β_2 -agonists, long-acting anticholinergics (not permitted before presentation), methylxanthines, heliox, and magnesium salts.

The study (Protocol 288) was conducted in conformance with Good Clinical Practice standards and was approved by ethical review committees or institutional review boards for each study site. Written informed consent/assent was obtained from each patient before any study procedures were performed.

Efficacy evaluations

The primary efficacy endpoint was the time-weighted average change in FEV_1 from prerandomization baseline during the first 60 minutes after drug

administration (ΔFEV_1 [0-60 minutes]). The percentage of patients with treatment failure, defined as patients who required hospitalization or for whom a decision to discharge was not made by 3 hours after administration of the drug, was a secondary endpoint. Other secondary endpoints included the total dose of as-needed β_2 -agonist and the number of β_2 -agonist administrations during 3 hours after drug administration; the time-weighted average ΔFEV_1 (0-40 minutes) and ΔFEV_1 (0-20 minutes); and the average change in FEV_1 after 10 minutes.

Spirometry readings were obtained using a standard spirometer (Spirotrac; Vitalograph Inc, Lenexa, Kan) supplied to each study site. The FEV_1 from at least 2, but preferably the 3 best, acceptable maneuvers were recorded. Spirometry was performed immediately before administering the study therapy (baseline) and at 10, 20, 40 minutes, and 1, 2, and 3 hours after the completion of study drug infusion and at the time the decision was made to discharge, admit, or discontinue the patient.

Safety evaluations

Safety and tolerability were assessed by clinical evaluations (physical examinations) and adverse experience (AE) monitoring. Safety analyses were based on the All-Patients-as-Treated population, including all randomized patients who started the study drug.

Statistical analysis

The primary hypothesis was that, in adult patients with acute asthma, the addition of intravenous montelukast 7 mg to standard therapy would cause a significant improvement in FEV_1 within the first 60 minutes after administration (ie, time-weighted average change in FEV_1 from preallocation baseline over the first 60 minutes after study drug administration), compared with placebo. The primary analysis was based on the Full Analysis Set population, which included all patients who started the study drug and who had at least 1 efficacy measurement at baseline and during the measurement period. FEV_1 endpoints were analyzed by using an analysis of covariance model with the baseline FEV_1 as a covariate, with factors for treatment, region (US/non-US site), and therapy before period I with systemic corticosteroids or leukotriene receptor antagonists (yes/no). Analyses of change from baseline at each time point were also performed by using the same analysis of covariance model. The percentages of treatment failures were compared by using a logistic model; analyses comparing the time to outcome were performed by using a Cox regression model. The dose of β_2 -agonist administered per patient and the total number of administrations in period II were assessed by using nonparametric analysis of variance models.

A prespecified step-down procedure was used to adjust for the multiplicity of endpoints.²⁰ Time of onset of action of montelukast was determined by comparing the time-weighted average difference from baseline in FEV_1 during the first 60, 40, 20 and 10 minutes, and each comparison was performed only if the previous one was significant at $\alpha = 0.01$. Analyses of the percentage of treatment failures was performed only if the comparison between treatments for the primary endpoint was significant at $\alpha = 0.01$. Because all other comparisons were considered secondary, no adjustments were needed. Subgroup analyses of the FEV_1 and treatment failure variables were performed for age (by tertiles), sex, race, and the 4 variables assessing asthma severity: baseline FEV_1 ($\leq$ / $>$ median), baseline dyspnea score, baseline respiratory rate ($\leq$ / $>$ median), and pulse oximetry ($\leq$ / $>$ median) to assess whether treatment effect was consistent across subgroups. Secondary and other endpoints were tested at the $\alpha = 0.05$ level.

A few *post hoc* analyses were performed. First, we computed the change in FEV_1 in period I before and after β_2 -agonist to benchmark the bronchodilating effect of montelukast against short-acting β_2 -agonist. Second, we examined the potential impact of baseline FEV_1 ($< 30\%$ predicted) on the primary endpoint. Third, we examined the potential impact of practice variation on the clinical endpoints. For these final analyses, we used a 2-level hierarchical model (with site as a random effect) to control better for practice variation across the 62 sites. We also examined treatment efficacy in a model in which the difference between proportions was the metric of choice; the model included site as a fixed effect (Cochran-Mantel-Haenszel tests).

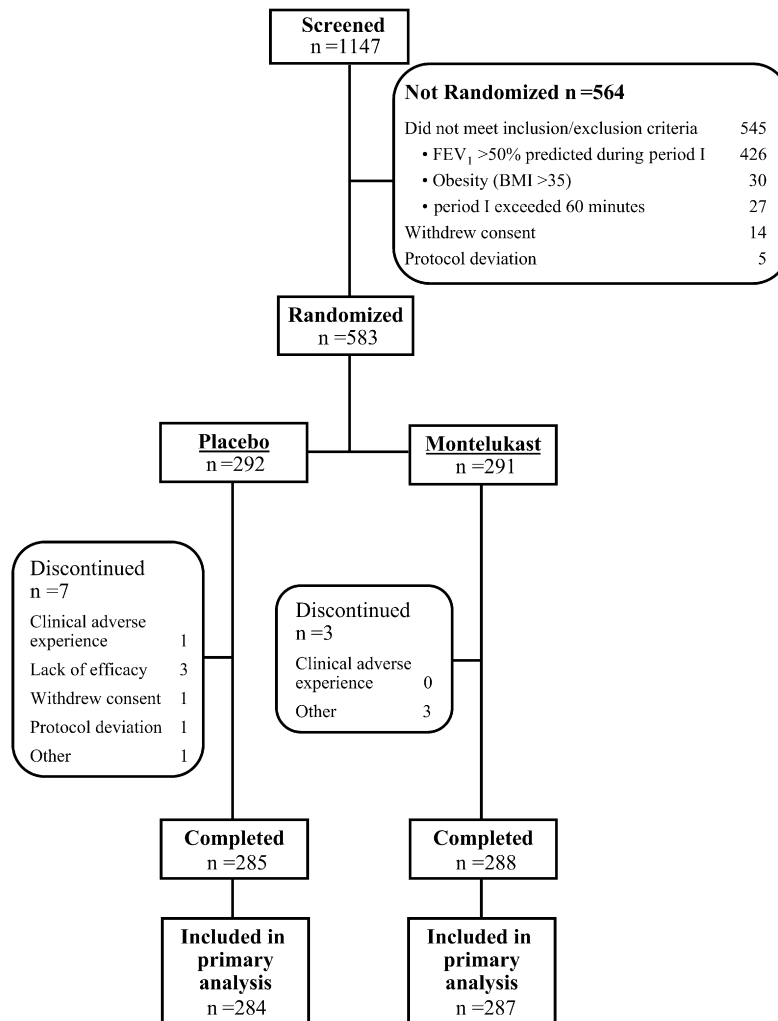


FIG 1. Patient flow in the study. *BMI*, Body mass index.

For a sample size of 275 patients/treatment arm, and assuming an SD of 0.34 L (and $\alpha = 0.05$), the study had 97% power to detect an effect size (mean treatment difference/pooled within-group SD) of 0.33 for montelukast compared with placebo in the primary endpoint.

RESULTS

Patients and baseline characteristics

Of 1147 patients screened, 583 were randomly assigned to treatment (Fig 1). A total of 573 patients (98%) completed the study. Of those randomized, 12 of 583 (2.1%; 4 montelukast, 8 placebo) were excluded from the primary analysis for not having a baseline FEV₁ measurement. Baseline characteristics of patients were similar between the treatment groups (Table I).

Efficacy

Compared with placebo, montelukast produced a significantly larger improvement of FEV₁ throughout the 2 hours after administration in time-specific analyses (Fig 2). A significant improvement was seen with montelukast in the primary endpoint of time-weighted average change in FEV₁ from preallocation

baseline during the first 60 minutes after administration (Δ FEV₁ [0-60 minutes]): the least squares (LS) mean difference between the 2 treatments was 0.10 L (95% CI, 0.04, 0.16; Table II). The median time-weighted percent changes in FEV₁ from preallocation baseline during the first 60 minutes after administration were 21.4% and 13.0% in the montelukast group and placebo group, respectively. Significant improvements were also seen in the secondary endpoints evaluating FEV₁ over 40, 20, and 10 minutes (Table II) and over 120 minutes (Fig 2).

The percentage of patients with treatment failure was slightly lower in the montelukast (26.8%) versus placebo (29.9%) group, but this difference was not statistically significant (Table III). Moreover, the additional secondary endpoints of total dose of β_2 -agonist administered per patient within 3 hours after drug administration and the number of administrations were not different between the 2 treatments (Table III).

Consistent with these results, the time-weighted average Δ FEV₁ (0-decision to discharge) was significantly greater in the montelukast group versus the placebo group (LS mean difference, 0.10; 95% CI, 0.04, 0.16; $P = .002$). The more subjective clinical endpoints—such as the time to treatment failure (hazard ratio [montelukast vs placebo]: 0.90; 95% CI, 0.66, 1.23), the time to

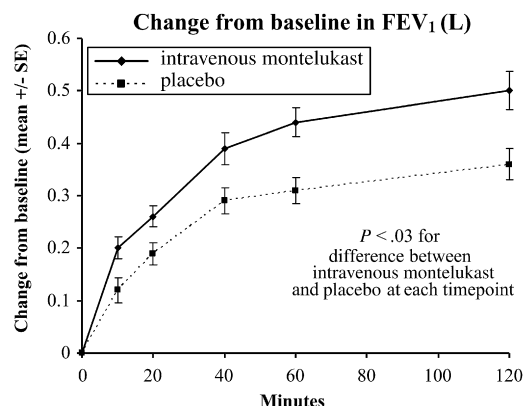
TABLE I. Baseline characteristics of patients

Characteristics	Placebo (n = 292)	Montelukast (n = 291)
Age (y) (range)	41.0 ± 15.3 (15-83)	41.1 ± 15.0 (15-82)
Sex, n (%)		
Male	117 (40)	138 (47)
Race/ethnicity, n (%)		
White	83 (28)	84 (29)
Black	96 (33)	101 (35)
Hispanic	92 (32)	80 (28)
Asian	13 (5)	17 (6)
Multiracial	7 (2)	8 (3)
Other	1 (0)	1 (0)
FEV ₁ (L)	1.2 ± 0.4	1.3 ± 0.4
FEV ₁ (% predicted)	36.7 ± 10.5	37.1 ± 10.4
Duration of asthma (y)	21.7 ± 14.7	21.3 ± 14.5
Frequency of asthma symptoms in past year, n (%)		
All year long without seasonal flares	90 (31)	96 (33)
All year with seasonal flares	95 (33)	94 (32)
Only during certain seasons	103 (35)	100 (34)
Frequency of asthma symptoms in past month, n (%)		
Never	17 (6)	31 (11)
≤2 times/wk	79 (27)	70 (24)
>2 times/wk	94 (32)	72 (25)
Continuously	32 (11)	31 (11)
Every day	66 (23)	86 (30)
Missing	4 (1)	1 (0)
No. of oral corticosteroid courses because of worsening asthma in the past year, n (%)		
0 courses	116 (41)	103 (36)
1 to <5 courses	118 (42)	137 (47)
5 to <10 courses	31 (11)	29 (10)
≥10 courses	19 (7)	20 (7)
Stratification factor of systemic CS or LTRA use before period I, yes, n (%)		
CS only	18 (6)	17 (6)
LTRA only	26 (9)	18 (6)

CS, Corticosteroid; LTRA, leukotriene receptor antagonist.
Unless otherwise specified, values are means ± SDs.

decision of discharge to home (hazard ratio, 1.12; 95% CI, 0.93, 1.34), and the time to decision for hospitalization (hazard ratio, 0.80; 95% CI, 0.55, 1.16)—were not significantly different between the 2 treatments.

Treatment effects for the primary endpoint (Δ FEV₁ [0-60 minutes]) were consistent for the prespecified subgroups of baseline FEV₁ ($\leq$ or $>$ median of 1.19 L), region (US versus non-US site), and therapy before period I with systemic corticosteroids or leukotriene receptor antagonists. (These 3 factors were in the main multivariate analysis.) Likewise, intravenous montelukast produced better FEV₁ results than placebo in prespecified subgroups according to age, sex, race, baseline dyspnea score, baseline respiratory rate, and baseline pulse oximetry. Although the treatment-by-subgroup interaction was not statistically significant, the treatment effect (montelukast minus placebo) for Δ FEV₁ (0-60 minutes) appeared larger in the subgroup with baseline FEV₁ >1.19 L (n = 282; LS mean, 0.14 L; 95% CI, 0.06,

FIG 2. Change from baseline in FEV₁ (L) over time (means ± SEs).

0.22) versus the subgroup with baseline FEV₁ ≤ 1.19 L (n = 289; LS mean, 0.06 L; 95% CI, -0.02, 0.15).

In other analyses, we explored treatment differences between montelukast and placebo for the treatment failure endpoint. Among patients with baseline FEV₁ >1.19 L, patients on montelukast tended to have fewer treatment failures (odds ratio [OR], 0.67; 95% CI, 0.37, 1.23); among patients with baseline FEV₁ ≤ 1.19 L, the OR was 1.03 (95% CI, 0.64, 1.65). Among 318 patients from US sites, those on montelukast tended to have fewer treatment failures (OR, 0.67; 95% CI, 0.40, 1.10), whereas among 265 patients from non-US sites, there was no apparent benefit (OR, 1.10; 95% CI, 0.65, 1.85). Finally, montelukast treatment produced a marked reduction in treatment failure among the 79 patients reporting yes for previous therapy with systemic corticosteroids or leukotriene-receptor antagonists (OR, 0.30; 95% CI, 0.11, 0.79), whereas it had no apparent effect among the 504 patients reporting no (OR, 1.04; 95% CI, 0.70, 1.53). This treatment-by-subgroup interaction was statistically significant ($P = .02$).

Post hoc analyses

The first *post hoc* analysis was done to benchmark the bronchodilating effect of montelukast against that of short-acting β_2 -agonist. This analysis showed that the mean difference ($\pm$ SE) between montelukast and placebo in Δ FEV₁ (0-60 minutes) of 0.10 L $\pm$ 0.03 L for patients in period II (regardless of short-acting β_2 -agonist use prerandomization) was on the same order of magnitude change in FEV₁ as that as a result of the administration of β_2 -agonist in the prerandomization period (0.12 L $\pm$ 0.02 L).

A second analysis examined the potential impact of baseline FEV₁ $<30\%$ and $\geq 30\%$ predicted. The treatment effect for average Δ FEV₁ (0-60 minutes) appeared larger in patients with baseline predicted FEV₁ $\geq 30\%$ (n = 419; difference in LS means, 0.13 L; 95% CI, 0.06, 0.20) than in patients with baseline predicted FEV₁ $<30\%$ (n = 152; difference, 0.04 L; 95% CI, -0.07, 0.15). There also appeared to be a lower risk of treatment failure for montelukast (compared with placebo) in patients with baseline predicted FEV₁ $\geq 30\%$ (OR, 0.73; 95% CI, 0.46, 1.16) versus patients with baseline predicted FEV₁ $<30\%$ (OR, 1.27; 95% CI, 0.67, 2.42).

In the final set of *post hoc* analyses, we examined the potential impact of practice variation on the clinical endpoints of treatment failure and hospitalization. In the full dataset, a mixed model modestly decreased the montelukast to placebo OR for treatment

TABLE II. Effect of treatment on FEV₁ at various times after drug administration

	Standard care + placebo				Standard care + montelukast				Treatment difference for change from baseline (montelukast minus placebo)
	n	Baseline (L), mean ± SD	Change from baseline (L), LS mean (95% CI)	Median % change†	n	Baseline (L), mean ± SD	Change from baseline (L), LS mean (95% CI)	Median % change†	LS mean (L) (95% CI)
Time-weighted ΔFEV ₁ (0-60 min)	284	1.21 ± 0.45	0.22 (0.17, 0.27)	13.0	287	1.26 ± 0.45	0.32 (0.27, 0.37)	21.4	0.10 (0.04, 0.16)**
Time-weighted ΔFEV ₁ (0-40 min)	283	1.21 ± 0.45	0.18 (0.13, 0.23)	10.3	287	1.26 ± 0.45	0.28 (0.23, 0.33)	17.6	0.09 (0.04, 0.15)**
Time-weighted ΔFEV ₁ (0-20 min)	282	1.21 ± 0.45	0.15 (0.10, 0.20)	6.7	287	1.26 ± 0.45	0.23 (0.19, 0.28)	13.1	0.09 (0.03, 0.14)*
ΔFEV ₁ at 10 min	260	1.20 ± 0.44	0.12 (0.06, 0.17)	4.1	269	1.25 ± 0.45	0.20 (0.15, 0.26)	10.4	0.08 (0.02, 0.15)*

P* ≤ .01, for montelukast vs placebo*P* ≤ .001 for montelukast vs placebo.†Median time-weighted average % change in FEV₁.

failure from 0.92 to 0.81 (95% CI, 0.54, 1.20). Stratifying by center, the difference in proportion with treatment failure (montelukast minus placebo) was almost significant: −4.8% (95% CI, −10.8, 1.2).

Better control for site-to-site variation using a 2-level hierarchical model yielded a montelukast-to-placebo OR for hospitalization of 0.66 (95% CI, 0.41, 1.07). Stratifying by center, the difference in proportion with hospitalization (montelukast minus placebo) was −7.9% (95% CI, −10.4, −0.6; *P* < .05). This statistically significant decrease in hospitalization for patients on montelukast compared with placebo was not present at non-US sites (difference in proportion, −1.5%; 95% CI, −7.7, 4.8); it was driven by a clinically and statistically significant reduction in hospitalization at US sites (difference in proportion, −7.0%; 95% CI, −16.3, −1.53; *P* < .05).

Safety

No significant differences were detected between the montelukast and placebo groups in the percentage of patients with 1 or more clinical AEs (19.6% vs 20.2%, respectively), drug-related AEs (0% vs 0%), serious AEs (9.6% vs 8.9%), or AEs leading to discontinuation from the study (0% vs 0.3%). Laboratory AEs were infrequent, and the percentage of patients experiencing 1 or more was similar among the treatment groups (3.6% vs 1.6%). Of note, a laboratory sample was collected only at the time of discharge or admission to the hospital; no comparison to baseline values was possible.

DISCUSSION

In this randomized, double-blind, placebo-controlled study of almost 600 adults with acute asthma, we found that intravenous montelukast, when added to standard therapy, provided significant, rapid, and sustained benefit in acute asthma, as indicated by relief of airway obstruction. The average changes in FEV₁ during the first 60 minutes (primary endpoint), at 120, 40, 20, and 10 minutes, and over the time interval until a disposition decision was made were all significantly greater with montelukast than with placebo. The treatment effect on FEV₁ seen at 10 minutes

TABLE III. Outcomes of secondary endpoints assessing treatment failure or β-agonist use

Endpoint	Standard care + placebo (n = 284)	Standard care + montelukast (n = 287)	Treatment effect
	No. (%)	No. (%)	OR for montelukast/placebo (95% CI)*
Treatment failures	85 (29.9)	77 (26.8)	0.92 (0.63, 1.34)
Patients hospitalized	62 (21.8)	49 (17.1)	
Patients for whom decision to discharge home was not reached by 3 h	23 (8.1)	28 (9.8)	
	Median (Q1-Q3)	Median (Q1-Q3)	Difference of medians (95% CI)
β-Agonist use**			
Total dose (mg)	5.0 (0.9-10.0)	5.0 (1.0-10.0)	0 (0, 0)
No. of treatments	2 (1-4)	2 (1-3)	0 (0, 0)

*OR < 1 favors montelukast.

**During 3-h period after administration of study drug.

is consistent with an early onset of action of intravenous montelukast and suggests a rapid improvement of lung function.

The fact that no significant differences were seen between the treatment groups in inhaled β₂-agonist use indicates that the difference in FEV₁ between montelukast and placebo appears to be an effect of montelukast alone and is not attributable to the use of concomitant therapy with β₂-agonist. A *post hoc* analysis showed that the treatment effect of montelukast on FEV₁ was of the same order of magnitude as that of β₂-agonist before study drug administration, suggesting that the bronchodilating effect of montelukast is clinically meaningful and, furthermore, may be of particular benefit to those patients with a limited response to inhaled short-acting β₂-agonists.

These results confirm and extend previous studies of intravenous montelukast. In patients with chronic asthma, intravenous

montelukast 7 mg provided significant improvement in FEV₁, compared with placebo, at the earliest time point measured (15 minutes).¹³ Although intravenous montelukast showed a more rapid onset of action than one would expect with oral montelukast, the extent of bronchodilation, as measured by FEV₁, AUC_{0-24 hours} and comparisons at individual time points, was similar to what has been reported for the oral formulation. Bronchodilation was long-lasting—up to 24 hours—after dosing with intravenously administered montelukast and similar to that for the oral formulation, although they were not directly compared in this study.

The observed FEV₁ improvement is consistent with results from a dose-ranging study of 201 patients with acute asthma.¹⁴ In that study, intravenous montelukast 7 mg or 14 mg added to standard care significantly improved FEV₁ within 20 minutes, compared with placebo; the improvement in bronchodilation persisted for at least 2 hours after intravenous therapy. Improvement in FEV₁ and reduction in leukotriene E₄ excretion were also correlated. Although statistical power was limited, patients who received montelukast had nonsignificant reductions in treatment failures and tended to receive less β_2 -agonist.¹⁴

In the current study, the secondary endpoint assessing treatment failure was not significantly different between the montelukast and placebo groups. Limitations of this clinical endpoint in a multicenter international study must be recognized insofar as nonclinical factors frequently contribute to disposition decisions. These include patient-centered factors such as time of arrival in the emergency department, age and sex of patient, availability of assistance at home, insurance status, cultural expectations, and need for disease-related education, as well as institutional determinants such as degree of bed use, timeliness of clinical evaluation, racial/ethnic bias, and need for discharge preparation.^{18,21-26} Overall, it is unlikely that criteria toward discharge or hospital admission of patients with asthma will be uniform across medical centers and regions, even when clinical standards are supposedly consistent. Our prespecified subgroup analysis of treatment failure comparing US versus non-US regions supports this view. Moreover, in a *post hoc* analysis using a statistical approach that better controlled for site-to-site differences, intravenous montelukast actually led to a significant reduction in asthma hospitalization compared with placebo. We caution investigators who are planning multicenter studies of novel treatments for acute asthma about the complexity of using treatment failure or hospitalization as endpoints. To demonstrate benefit for these clinical endpoints, it is critical to standardize admission practices or to limit sites to those with very similar practice patterns.

In other subgroup analyses, our results suggested that patients with a higher baseline FEV₁ might experience a larger treatment effect of montelukast on FEV₁ and a potentially lower risk of treatment failure. Several investigators define a baseline predicted FEV₁ of <30% as indicative of a greater severity of acute asthma.²⁷⁻²⁹ *Post hoc* analyses suggested that among these patients with FEV₁ ≤50%, montelukast reduced treatment failure and hospitalization to a larger extent in those patients with a baseline predicted FEV₁ of ≥30%. All these subgroup results, although preliminary and thus needing confirmation, suggest that montelukast may have some benefit in improving airflow and reducing treatment failures and hospitalizations in patients with severe, but not excessively severe, exacerbations.

In conclusion, intravenous montelukast added to standard care produced significant and sustained relief of airway obstruction throughout the 2 hours after drug administration, with an onset of

action as early as 10 minutes. Montelukast was generally well tolerated, and its safety profile was comparable to that of placebo. Further studies are needed to assess fully the likely benefits of intravenous leukotriene modifiers as a treatment option for acute asthma.

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Clinical implications: Current treatments for acute asthma provide inadequate benefit for some patients. Adding intravenous montelukast to standard care in adults with acute asthma produced early and sustained improvement in lung function.

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