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 FEV₁ ≤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 FEV₁ during 60 minutes after drug administration. Secondary endpoints included the time-weighted average change in FEV₁ 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 FEV₁ 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 FEV₁-related variables were seen at all time points (all P <0.05). 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, FEV₁, 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, β₂-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 β₂-agonist bronchodilators or corticosteroids provides added benefit.10-12 Dockhorn et al13 showed that intravenous montelukast improved FEV₁ in patients with chronic asthma, and Camargo et al14 found that the addition of intravenous montelukast to standard care produced a rapid improvement in FEV₁ in acute asthma. A role for montelukast in acute asthma was supported by the observation of increased urinary leukotriene E₄ 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 FEV₁ 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
treatment of acute asthma. The primary endpoint of the study was change in lung function (FEV₁).

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 FEV₁ reversibility ≥15% after β₂-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. On arrival, patients received standard treatment during a ≤60-minute screening period (period I): oxygen, inhaled short-acting β₂-agonist (2.5-5.0 mg in 3 mL saline every 20 minutes) as needed, and inhaled ipratropium (not to exceed 36 μg per hour) or nebulized ipratropium (not to exceed 500 μg per hour) as needed. Patients with FEV₁ ≤50% predicted on all measurements were allocated (1:1) to double-blind therapy (according to a computer-generated randomized 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 diltiazem 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, β₂-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 II. Additional medications were not permitted during periods I and II, including inhaled corticosteroids, long-acting β₂-agonists, long-acting anticholinergics (not permitted before presentation), methylxanthenes, 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 FEV₁ from prerandomization baseline during the first 60 minutes after drug administration (ΔFEV₁ [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 β₂-agonist and the number of β₂-agonist administrations during 3 hours after drug administration; the time-weighted average ΔFEV₁ (0-40 minutes) and ΔFEV₁ (0-20 minutes); and the average change in FEV₁ after 10 minutes.

Spirometry readings were obtained using a standard spirometer (Spirotron; Vitalograph Inc, Lenexa, Kan) supplied to each study site. The FEV₁ 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 FEV₁ within the first 60 minutes after administration (ie, time-weighted average change in FEV₁ from prerandomization 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. FEV₁ endpoints were analyzed by using an analysis of covariance model with the baseline FEV₁ 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 β₂-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. Time of onset of action of montelukast was determined by comparing the time-weighted average difference from baseline in FEV₁ during the first 60, 40, 20 and 10 minutes, and each comparison was performed only if the previous one was significant at α = 0.01. Analyses of the percentage of treatment failures were performed only if the comparison between treatments for the primary endpoint was significant at α = 0.01. Because all other comparisons were considered secondary, no adjustments were needed. Subgroup analyses of the FEV₁ and treatment failure variables were performed for age (by tertiles), sex, race, and the 4 variables assessing asthma severity: baseline FEV₁ (</> median), baseline dyspnea score, baseline respiratory rate (</> median), and pulse oximetry (</> median) to assess whether treatment effect was consistent across subgroups. Secondary and other endpoints were tested at the α = 0.05 level.

A few post hoc analyses were performed. First, we computed the change in FEV₁ in period I before and after β₂-agonist to benchmark the bronchodilating effect of montelukast against short-acting β₂-agonist. Second, we examined the potential impact of baseline FEV₁ (</>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 weights).
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 FEV$_1$ measurement. Baseline characteristics of patients were similar between the treatment groups (Table I).

Efficacy

Compared with placebo, montelukast produced a significantly larger improvement of FEV$_1$ 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 FEV$_1$ from preallocation baseline during the first 60 minutes after administration ($\Delta$FEV$_1$ [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 FEV$_1$ 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 FEV$_1$ 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 $\beta_2$-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 $\Delta$FEV$_1$ (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...
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 (ΔFEV1 [0-60 minutes]) were consistent for the prespecified subgroups of baseline FEV1 (≤ 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 ΔFEV1 (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, 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 β2-agonist. This analysis showed that the mean difference (±SE) between montelukast and placebo in ΔFEV1 (0-60 minutes) of 0.10 L ± 0.03 L for patients in period II (regardless of short-acting β2-agonist use prerandomization) was on the same order of magnitude change in FEV1 as that as a result of the administration of β2-agonist in the prerandomization period (0.12 L ± 0.02 L).

A second analysis examined the potential impact of baseline FEV1 <30% and ≥30% predicted. The treatment effect for average ΔFEV1 (0-60 minutes) appeared larger in patients with baseline predicted FEV1 ≥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 ≥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

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**TABLE I. Baseline characteristics of patients**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Placebo (n = 292)</th>
<th>Montelukast (n = 291)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y) (range)</td>
<td>41.0 ± 15.3 (15-83)</td>
<td>41.1 ± 15.0 (15-82)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>117 (40)</td>
<td>138 (47)</td>
</tr>
<tr>
<td>Race/ethnicity, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>83 (28)</td>
<td>84 (29)</td>
</tr>
<tr>
<td>Black</td>
<td>96 (33)</td>
<td>101 (35)</td>
</tr>
<tr>
<td>Hispanic</td>
<td>92 (32)</td>
<td>80 (28)</td>
</tr>
<tr>
<td>Asian</td>
<td>13 (5)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>Multiracial</td>
<td>7 (2)</td>
<td>8 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (0)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>FEV1 (L)</td>
<td>1.2 ± 0.4</td>
<td>1.3 ± 0.4</td>
</tr>
<tr>
<td>Duration of asthma (y)</td>
<td>21.7 ± 14.7</td>
<td>21.3 ± 14.5</td>
</tr>
<tr>
<td>Frequency of asthma symptoms in past year, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All year long without seasonal flares</td>
<td>90 (31)</td>
<td>96 (33)</td>
</tr>
<tr>
<td>All year with seasonal flares</td>
<td>95 (33)</td>
<td>94 (32)</td>
</tr>
<tr>
<td>Only during certain seasons</td>
<td>103 (35)</td>
<td>100 (34)</td>
</tr>
<tr>
<td>Frequency of asthma symptoms in past month, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>17 (6)</td>
<td>31 (11)</td>
</tr>
<tr>
<td>≤2 times/wk</td>
<td>79 (27)</td>
<td>70 (24)</td>
</tr>
<tr>
<td>&gt;2 times/wk</td>
<td>94 (32)</td>
<td>72 (25)</td>
</tr>
<tr>
<td>Continuously</td>
<td>32 (11)</td>
<td>31 (11)</td>
</tr>
<tr>
<td>Every day</td>
<td>66 (23)</td>
<td>86 (30)</td>
</tr>
<tr>
<td>Missing</td>
<td>4 (1)</td>
<td>1 (0)</td>
</tr>
<tr>
<td>No. of oral corticosteroid courses because of worsening asthma in the past year, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 courses</td>
<td>116 (41)</td>
<td>103 (36)</td>
</tr>
<tr>
<td>1 to &lt;5 courses</td>
<td>118 (42)</td>
<td>137 (47)</td>
</tr>
<tr>
<td>5 to &lt;10 courses</td>
<td>31 (11)</td>
<td>29 (10)</td>
</tr>
<tr>
<td>≥10 courses</td>
<td>19 (7)</td>
<td>20 (7)</td>
</tr>
<tr>
<td>Stratification factor of systemic CS or LTRA use before period I, yes, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CS only</td>
<td>18 (6)</td>
<td>17 (6)</td>
</tr>
<tr>
<td>LTRA only</td>
<td>26 (9)</td>
<td>18 (6)</td>
</tr>
</tbody>
</table>

CS, Corticosteroid; LTRA, leukotriene receptor antagonist.

Unless otherwise specified, values are means ± SDs.
TABLE II. Effect of treatment on FEV1 at various times after drug administration

<table>
<thead>
<tr>
<th>Time-weighted ΔFEV₁ (0-60 min)</th>
<th>Baseline (L), mean ± SD</th>
<th>Change from baseline (L), LS mean (95% CI)</th>
<th>Median % change†</th>
<th>Treatment difference for change from baseline (montelukast minus placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard care + placebo</td>
<td>284 1.21 ± 0.45 0.22 (0.17, 0.27)</td>
<td>13.0</td>
<td></td>
<td>287 1.26 ± 0.45 0.32 (0.27, 0.37) 21.4 0.10 (0.04, 0.16)**</td>
</tr>
<tr>
<td></td>
<td>283 1.21 ± 0.45 0.18 (0.13, 0.23)</td>
<td>10.3</td>
<td></td>
<td>287 1.26 ± 0.45 0.28 (0.23, 0.33) 17.6 0.09 (0.04, 0.15)**</td>
</tr>
</tbody>
</table>

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

TABLE III. Outcomes of secondary endpoints assessing treatment failure or β₂-agonist use

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Standard care + placebo (n = 284)</th>
<th>Standard care + montelukast (n = 287)</th>
<th>Treatment difference for montelukast/ placebo (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failures</td>
<td></td>
<td></td>
<td>0.92 (0.63, 1.34)</td>
</tr>
<tr>
<td>Patients hospitalized</td>
<td>62 (21.8)</td>
<td>49 (17.1)</td>
<td></td>
</tr>
<tr>
<td>Patients for whom decision to discharge home was not reached by 3 h</td>
<td>23 (8.1)</td>
<td>28 (9.8)</td>
<td></td>
</tr>
</tbody>
</table>

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

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 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). 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, AUC₀₋₂₄ hours, 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. 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 β₂-agonist.

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. 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. 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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