A Randomized Controlled Trial of Intravenous Montelukast in Acute Asthma

Carlos A. Camargo, Jr., Howard A. Smithline, Marie-Pierre Malice, Stuart A. Green, and Theodore F. Reiss

Department of Emergency Medicine, Massachusetts General Hospital, and Channing Laboratory, Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston; Department of Emergency Medicine, Baystate Medical Center, Springfield, Massachusetts; and Respiratory and Allergy, Merck Research Laboratories, Rahway, New Jersey

Many patients with acute asthma do not respond adequately to currently accepted therapy, including oxygen, β-agonists, and corticosteroids. Leukotriene receptor antagonists such as montelukast have demonstrated efficacy in chronic asthma, but their efficacy in acute asthma is unknown. In this randomized, double-blind, parallel-group pilot study, adults with moderate to severe acute asthma received standard therapy plus either intravenous montelukast (7 or 14 mg) or matching placebo. A total of 201 patients were randomized, and 194 had complete data available for analysis. There was no difference in FEV1 response between the 7- and 14-mg montelukast groups. Montelukast improved FEV1 over the first 20 minutes after intravenous administration (mean percentage change from prerandomization baseline, 14.8% versus 3.6% for the pooled montelukast and placebo treatment groups, respectively; p = 0.007). This benefit was observed at 10 minutes and over 2 hours after intravenous therapy. Patients treated with montelukast tended to receive less β-agonists and have fewer treatment failures than patients receiving placebo. The tolerability profile for montelukast was similar to that observed for placebo, and no unexpected adverse experiences were observed. We conclude that intravenous montelukast in addition to standard therapy causes rapid benefit and is well tolerated in adults with acute asthma.

Keywords: leukotriene antagonists; injections, intravenous; exacerbation

Acute asthma consistently ranks among the most frequent causes of emergency department visits in children and adults and is a major contributor to time away from work, with an estimated two-million emergency department visits and 500,000 hospital admissions annually (1–5). Furthermore, acute asthma may account for a disproportionate share of direct asthma costs; in one study of asthma resource use, hospitalizations accounted for 3.8% of total asthma encounters, but they comprised 44.6% of asthma costs (6).

Treatment goals for acute asthma include correction of significant hypoxemia, rapid reversal of airflow obstruction, and reduction in the likelihood of recurrent severe airflow obstruction (7–9). Currently accepted initial therapy for acute asthma includes oxygen and short-acting β-agonist bronchodilators; in addition, systemic corticosteroids should be considered for those patients who are severely ill at presentation or who fail to respond to initial measures. However, up to 30% of patients who present with acute asthma will fail to respond adequately to short-acting β-agonists (10), and benefit from systemic corticosteroids is not generally observed for 4–6 hours or longer (11). As a result, current therapeutic options for acute asthma do not adequately address treatment goals for a substantial number of patients.

Montelukast is a leukotriene receptor (CysLT1) antagonist that when administered orally is effective in the management of chronic asthma (12). Given as a single intravenous bolus infusion to patients with chronic asthma, montelukast causes significant benefit (measured as change in FEV1 from baseline) within 15 minutes, and this effect is sustained for at least 24 hours (13). In this multicenter, randomized, placebo-controlled pilot study, we compared the clinical efficacy, safety, and tolerability of intravenous montelukast administered in addition to standard therapy with that of standard therapy alone in the management of acute exacerbations of asthma. We hypothesized that in adult patients with acute asthma, the addition of montelukast to standard therapy would cause a rapid improvement in airflow obstruction (as measured by improvement in FEV1) as well as improvement in clinically relevant outcomes such as hospitalization or requirement for prolonged or additional antiasthma therapy.

METHODS

Patients

Sixteen U.S. sites participated in this study, primarily emergency departments that were affiliated with academic medical centers. Adults who were 15–54 years old and who were presenting with acute asthma were screened for enrollment. For the purposes of this pilot study, patients were required to have the following: a history of asthma for at least 1 year, a history of tobacco use of less than 10 pack-years, and no concomitant therapy with systemic corticosteroids, leukotriene modifiers, anticholinergics, or long-acting β-agonist bronchodilators. Patients with pneumonia, congestive heart failure, or other clinical explanations for dyspnea were excluded, as were patients with significant comorbid disorders requiring acute management. The study protocol was approved by each investigator’s respective institutional review board, and all patients gave written informed consent to participate.

Study Design

This was a multicenter, double-blind (with in-house blinding procedures), randomized, placebo-controlled parallel group study consisting of a screening period and an active study period. The screening period began when the patient arrived at the study site and ended when the patient received study medication (maximum duration, 60 minutes). During the screening period and before consenting to the study, patients could be treated with short-acting β-agonists (albuterol, 2.5 mg by nebulizer) and oxygen. Once informed consent was obtained, patients underwent an initial spirometry (Puritan Bennett model PB-100), followed by a mandatory albuterol nebulization and a second spirometry. Each spirometry was performed and interpreted in accordance with the reproducibility and acceptability criteria of the American Thoracic Society (14). Patients in whom the FEV1 was greater than 70% of the predicted value (15) on either spirometry were excluded. In addition,
patients were excluded if the FEV1 (expressed as a percentage of the predicted value) increased or decreased by greater than or equal to 20 percentage points between the two measurements. Patients who met the eligibility criteria were allocated by means of a blinded computer-generated randomization schedule with a blocking factor of six to receive study medication. Allocation numbers were encoded on labels included with the study drug, and patients were assigned the next available allocation number in sequence at each site. Patients, investigators, and the in-house research team were not aware of actual treatment at any point during the study. The allocation code was not broken until after the study was completed and the dataset was declared final.

Two doses of intravenous montelukast (7 and 14 mg; Merck and Co., Inc., Whitehouse Station, NJ) were evaluated. Previous studies have shown that 7-mg intravenous montelukast yielded a single dose, plasma concentration area under the curve (AUC) profile comparable to the approved 10-mg oral montelukast tablet (16). Although there has been no additional clinical efficacy in chronic asthma evident at oral montelukast doses above 10 mg (17), in this study, the 14-mg dose of montelukast was included in addition to 7 mg to demonstrate that dose-related efficacy did not occur in acute asthma.

Intravenous montelukast (7 or 14 mg) or exact matching placebo was supplied as a lyophilized powder together with diluent (3.3% dextrose/0.3% normal saline). The study drug was reconstituted by a qualified individual not otherwise involved with the care of the patient and was administered as a manual bolus over 5 minutes. Serial spirometries were performed at 10, 20, 40, 60, and 120 minutes and at 3 and 6 hours after intravenous study drug infusion. After the 20-minute spirometry, patients who were deemed eligible for discharge, who were admitted to the hospital, or who withdrew from the study were not required to perform the subsequent measurements. Corticosteroids and additional short-acting β-agonists were given as needed after the 20-minute spirometry. When indicated, corticosteroids were administered as a standard dose (prednisone, 60 mg orally).

All patients successfully discharged from the emergency setting were given a standard course of oral prednisone (50 mg/day × 5 days) and were scheduled for a follow-up visit 14 ± 3 days later. This standardized outpatient course of prednisone was not counted when accounting for concomitant corticosteroids received during the active treatment period.

Urinary Leukotriene E4 Measurements

Urine samples were obtained during the acute treatment period and in addition at a follow-up visit 2 weeks later for those patients successfully discharged from the study site. Urinary leukotriene E4 (LTE4) was analyzed by reversed-phase liquid chromatography after precolumn extraction combined with radioimmunoassay as described elsewhere (18). Results were normalized to the creatinine concentration determined in the same sample.

Evaluations and Statistical Analyses

The primary endpoint of the study was the average percentage change in FEV1 from predose baseline at 20 minutes after study medication infusion. The predose baseline FEV1 was defined as the FEV1, which immediately preceded randomization and study drug administration (i.e., the second spirometry in the screening period described previously here). The analytic plan called for the pooling of the 7- and 14-mg montelukast treatment group results if no between-dose differences on the primary endpoint were found. All FEV1 analyses were performed using an analysis of covariance model, with baseline FEV1 as covariate, and significance was imparted at the p ≤ 0.05 level. Shapiro-Wilk test statistics were used to test for normality. Levene’s test was used to test for homogeneity of variances. Secondary endpoints included the proportion of patients in each treatment group who were determined to be treatment failures (defined as hospitalizations, need for an “excluded” medication, or need for greater than 6 hours of active treatment after study drug administration). Excluded medications included the following: inhaled corticosteroids; open-label leukotriene modifiers; long-acting β-agonists; inhaled cromolyn; oral, subcutaneous, or intravenous β-agonists; parenteral or rectal xanthine derivatives or combinations; inhaled anticholinergic agents; halothane; helium–oxygen mixtures; or magnesium salts. Other prespecified secondary endpoints included the proportion of patients receiving corticosteroids and the number of β-agonist treatments received during the active treatment period. An additional analysis was performed on the number of patients who received more than two β-agonist treatments after intravenous administration of the study drug. Percentages of treatment failures, percentages of patients receiving corticosteroids, and percentages of patients receiving two or more β-agonists were compared using Fisher’s exact test. A logistic model was also used to compare the percentage of treatment failures; the model including baseline FEV1 and patient characteristics as covariates. The average number of doses of β-agonist administered per patient while in the emergency department was compared between the treatment groups using a nonparametric analysis of variance. All analyses followed the intention-to-treat approach. All patients with at least one prerandomization and at least one treatment FEV1 measure were included in the FEV1 analyses. In the analysis of the average percentage changes from baseline in FEV1, if data at a time point were missing, no value was carried forward. In the analysis of percent changes from baseline in FEV1 at the different time points (10, 20, 40, 60, and 120 minutes), if any FEV1 measurement was not available within the time interval (0, 120 minutes), then the last available post-treatment measurement before the missing value was used instead.

Based on the results of a previous study (13), a sample size of 195 patients (130 receiving intravenous montelukast and 65 receiving placebo) gave 80% power to detect an 11 percentage point difference on the primary endpoint (the average percentage change in FEV1 from predose baseline and in the pooled montelukast groups and placebo, assuming a SD of 25 percentage points.

RESULTS

A total of 274 patients were screened for enrollment, and 201 were randomized to receive study medication. A summary flow diagram of patients enrolled in the study is depicted in Figure 1. The major reason for exclusion was failure to meet spirometric criteria (57 of 73 patients [78%]). Of these, 49 were excluded because of an FEV1 of more than 70% of the predicted value (before or after albuterol), whereas eight were excluded because of an increase in FEV1 (expressed as percent predicted value) of more than 20 percentage points after an albuterol nebulization.

Baseline characteristics of randomized patients are presented in Table 1. The treatment groups were comparable with respect to age, sex, smoking history, age at asthma diagnosis, history of atopy, and other clinical characteristics associated with asthma.

Most patients allocated in the study had moderate to severe asthma exacerbations (FEV1 of less than 50–60% of the predicted value) (19). Initial FEV1 (generally determined after one albuterol treatments, according to the study design) was 39.2 ± 14.2% of the predicted value in the pooled montelukast groups and 46.4 ± 15.4% in the placebo group. The mean predose FEV1 (determined immediately before study drug administration) was 1.6 L, corresponding to 47% of the predicted value. The mean predose FEV1 was similar between patients receiving montelukast and placebo (1.6 ± 0.6 versus 1.7 ± 0.6 L, respectively).

Seven patients (two in the montelukast 7-mg group, three in the montelukast 14-mg group, and two in the placebo group) did not have valid FEV1 data for the 10- and 20-minute time points and were not included in the primary endpoint analyses. Three patients (one from each of the three treatment groups) were discontinued from the study for protocol violations after having received study drug (two due to discovery of concomitant medications taken before enrollment and one due to misinterpretation of baseline spirometry). However, these patients did have valid data for the primary endpoint and were included in the intention-to-treat analyses as prespecified in the protocol.

The FEV1 responses at each time point after study drug administration for the three treatment groups are shown in Figure 2. There was no difference in treatment effect between the groups receiving montelukast 7 or 14 mg. Compared with the group receiving standard therapy plus placebo, a significant
improvement in FEV₁ was observed among patients receiving standard therapy plus intravenous montelukast at the earliest time point measured (10 minutes; mean percent change in FEV₁ = 13.4% and 4.5% for pooled montelukast and placebo groups, respectively; least square mean difference was 8.0%; 95% confidence interval [CI], 0.9%, 15.1%; p = 0.03). Moreover, this benefit was maintained for at least 2 hours; the least square mean difference between the montelukast (pooled 7 and 14 mg doses) and placebo treatment groups at 2 hours was 14.1 percentage points with a 95% CI of 4.7%, 23.5% (p = 0.003).

As specified in the protocol, the primary endpoint was the average percent change in FEV₁ from preallocation baseline over the first 20 minutes after study drug administration. Combined with standard therapy, montelukast caused a significant improvement in FEV₁ over the first 20 minutes after intravenous administration compared with that observed in patients receiving placebo (the mean percentage change from preallocation baseline, 14.8% versus 3.6% for the pooled montelukast and placebo treatment groups, respectively; least square mean difference was 10%; 95% CI, 2.8%, 17.3%, p = 0.007). These values were 19.5% and 5.2%, respectively, over the first 60 minutes (least square mean difference of 13%; 95% CI, 5.2%, 20.7%; p = 0.001).

Figure 3 illustrates the distribution of FEV₁ responses (primary endpoint) observed for patients receiving either montelukast or placebo. A similar unimodal pattern of responses was observed for both groups, and there was no evidence of clearly defined “responders” and “nonresponders” to montelukast.

### TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS ENROLLED IN THE STUDY

<table>
<thead>
<tr>
<th></th>
<th>Montelukast IV (7 and 14-mg doses; n = 135)</th>
<th>Placebo (n = 66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>35.7 ± 10.4</td>
<td>34.5 ± 9.6</td>
</tr>
<tr>
<td>Female, %</td>
<td>56.3</td>
<td>60.6</td>
</tr>
<tr>
<td>Duration of asthma, yr</td>
<td>20.4 ± 12.7</td>
<td>19.8 ± 14.4</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>32.6</td>
<td>24.2</td>
</tr>
<tr>
<td>Allergic Rhinitis, %</td>
<td>57.0</td>
<td>54.5</td>
</tr>
<tr>
<td>Number of asthma-related ED visits in the past 12 months</td>
<td>3.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Baseline FEV₁, L</td>
<td>1.6 ± 0.6</td>
<td>1.7 ± 0.6</td>
</tr>
<tr>
<td>Baseline FEV₁, % predicted</td>
<td>44.8 ± 15.7</td>
<td>50.1 ± 15.5</td>
</tr>
</tbody>
</table>

*Definition of abbreviations: ED = Emergency Department; IV = Intravenous.

 BASELINE FEV₁ was defined as the preallocation measurement immediately preceding study drug administration (i.e., after initial treatment with oxygen and β-agonists).
Baseline factors, including demographics, asthma history, and duration of symptoms before presentation, were examined in an attempt to identify predictors of response to treatment; other than treatment group and baseline FEV₁, no factor was identified that explained the variability of the data (data not shown).

We considered that any improvement in FEV₁ attributable to montelukast might be confounded by alterations in postrandomization concomitant therapy between the groups. In fact, patients randomized to intravenous montelukast at either dose received corticosteroids less often than did those randomized to placebo (59.3% versus 75.8%, respectively; 95% CI for difference, −31.5, −1.9; p = 0.03; Figure 4). In addition, patients randomized to intravenous montelukast (either 7 or 14 mg) received numerically fewer β-agonist nebulizations (median = 1.0; 95% CI, 0.8, 1.2) than those randomized to placebo (median = 2.0; 95% CI, 1.5, 2.5; p = 0.42 by analysis of variance). Expressed differently, compared with placebo, a smaller proportion of patients in the montelukast group received two or more β-agonist treatments during the active treatment period (30.3% and 17.8%, respectively; 95% CI for difference, −28.5, 1.4; p = 0.048 by Fisher’s exact test; Figure 4). No other differences in concomitant therapy were observed between the groups.

Using data from the pooled montelukast doses, a trend toward a reduction in treatment failures was observed for montelukast versus placebo (11.1% versus 18.2%, respectively; 95% CI for difference, −22.6, 5.0; p = 0.19 by Fisher’s exact test; Figure 4). An exploratory analysis using a logistic model was performed to study the influence of baseline factors on the probability of treatment failures. Other than treatment allocation, baseline FEV₁ was found to be a significant (p < 0.001) factor.
predicting the occurrence of treatment failure; no other such factors were identified. When baseline FEV₁ was considered in the analysis of treatment failures, the benefit for montelukast was significant (odds ratio compared with placebo = 0.39; 95% CI, 0.15, 0.98; p = 0.046). There was no difference between patients receiving intravenous montelukast or placebo with regard to the frequency of unscheduled, asthma-related repeat visits to the emergency room, hospitalizations, doctor visits, or need for rescue corticosteroids in the 14-day period after discharge from the study site (15 of 109 [13.8%] for montelukast, 6 of 49 [12.2%] for placebo, p = NS).

To explore the mechanisms underlying asthma exacerbations, urinary LTE₄, (a stable metabolite of leukotriene metabolism) was measured. Urinary LTE₄ levels were increased during the asthma exacerbations, as compared with levels obtained 2 weeks later (median 102.4 versus 69.5 pg/mg creatinine, respectively; p = 0.009 by sign-rank test). There was no difference between treatment groups regarding this parameter. Although patients with higher LTE₄ levels tended to have greater FEV₁ improvements after montelukast, this did not reach statistical significance (p = 0.36).

Thirty-three of the 201 randomized patients (16.4%) were discontinued from the study during the acute treatment period: 9 of 68 (13.2%) in the 7-mg intravenous montelukast group, 9 of 67 (13.4%) in the 14-mg intravenous montelukast group, and 15 of 66 (22.7%) in the placebo group. These differences were not statistically different (p = 0.11 for intravenous montelukast versus placebo). Twenty-five of the 33 discontinuations (75.8%) were due to clinical adverse experiences, of which 20 were hospitalizations for asthma (six, six, and eight in the 7-mg montelukast, 14-mg montelukast, and placebo groups, respectively). In general, intravenous montelukast was well tolerated, with an adverse experience profile that was comparable to placebo. There were no unexpected adverse events. Two patients (one in the 14-mg montelukast group and one in the placebo group) noted catheter site discomfort during the study; in both cases, the symptoms were mild and self-limited, and no specific action was taken with regard to the study drug infusion.

**DISCUSSION**

In this study, intravenous montelukast compared with placebo was associated with a rapid benefit as evidenced by a significant improvement in FEV₁ within 10 minutes of administration. The benefit attributed to montelukast was not confounded by an increased use of β-agonists or corticosteroids and was accompanied by trends toward improvements in clinical outcomes such as treatment failures. Intravenous montelukast demonstrated a tolerability profile comparable to placebo, and no unexpected adverse experiences were noted.

Although many asthma exacerbations are resolved promptly, a substantial proportion (in particular patients presenting with moderate to severe exacerbations) will require prolonged therapy in an acute setting and/or hospitalization. For example, up to 30% of patients with acute asthma fail to respond adequately to short-acting β-agonists (10). Such patients typically receive systemic corticosteroids, but benefit from systemic corticosteroids is not generally observed for 4–6 hours or longer (11).

Several studies have examined new interventions in acute asthma that could provide rapid and sustained relief from airflow obstruction, in addition to current standard treatment. For example, inhaled ipratropium may provide a modest bronchodilator benefit and an improvement in hospital admission rates, particularly in patients with severe asthma exacerbations (20–22), and ipratropium is now used frequently for asthma in the acute setting (23). Others have suggested, however, that there is little if any added benefit of ipratropium above that of standard therapy with β-agonists (24). Moreover, anticholinergics do not appear to be effective for patients whose initial response to β-agonists is impaired (25), and at this point, there is no clear consensus regarding their use (24, 26). Other interventions for acute asthma that are current areas of active research include intravenous magnesium (27), xanthines (28), and inhaled helium/oxygen mixtures (29). Leukotriene pathways are activated in acute asthma, as evidenced by elevations in urinary leukotriene excretion reported elsewhere (30, 31) and confirmed in this study. The observations that corticosteroids do not inhibit leukotriene synthesis and activation and that the benefit of leukotriene modifiers is additive to corticosteroids, β-agonists, and theophylline in chronic asthma provide a strong rationale for exploring the potential additive benefit of leukotriene modifiers to current acute asthma treatment. In a preliminary report, the addition of a high dose (160 mg) of oral zafirlukast to standardized therapy for acute asthma including β-agonists and corticosteroids demonstrated a trend toward reduced adult hospital admissions from 15 to 10% (32).

A potential limitation to any study that examines an adjunctive treatment is the definition of the standard therapy used as the comparison. In this study, standard therapy included oxygen, β-agonist treatment, and at the investigator’s discretion, systemic corticosteroids consistent with current treatment guidelines (8, 9). Patients who were already receiving systemic corticosteroids and/or antileukotrienes before randomization were ex-
cluded. It is therefore conceivable that the benefit demonstrated for intravenous montelukast in this study might not be observed among subjects with asthma who have significant asthma exacerbations despite prior treatment with these therapies. Further studies are needed to evaluate the efficacy of intravenous montelukast in such patients.

Although many asthma exacerbations are rapidly reversed by short-acting β-agonists, a substantial proportion of patients with asthma require additional treatment. The additional benefit of continued β-agonists treatment for patients who do not demonstrate an adequate initial response to β-agonists is typically poor (33, 34). If not immediately hospitalized, such patients usually require several hours of additional emergency care in the hope that aggressive treatment with systemic corticosteroids will prevent the need for hospitalization. Because these patients are the most likely to benefit from an adjunctive therapy such as intravenous montelukast, this study was designed to identify patients whose initial response to β-agonists was less than adequate, as evidenced by a failure to demonstrate either a strong improvement in FEV1 or an FEV1 that was above a commonly accepted threshold (i.e., 70% of the predicted value). Indeed, the relative inadequacy of continued treatment with β-agonists and corticosteroids for patients with acute asthma who do not meet these initial response criteria is illustrated by the poor improvement in FEV1 observed for randomized patients receiving standardized therapy plus placebo (Figure 2). This study, if confirmed, suggests that montelukast may confer added benefit to current treatment options in the management of acute asthma.

Acknowledgment: The authors thank Dr. Rene Verbesselt for performing the LTE4 analyses. The following investigators also participated in this study: Leonard Altman, MD (Seattle, WA); Barry Brenner, MD, PhD (Brooklyn, NY); Thomas Burke, MD (Olympia, WA); Paul Cherwinsky, MD (North Dartmouth, MA); Rita Cydulka, MD (Cleveland, OH); Louis Graff, MD (New Britain, CT); Edward Kerwin, MD (Medford, OR); Richard F. Lockey, MD (Tampa, FL); Richard M. Nowak, MD (Detroit, MI); Brian O’Neil, MD (Detroit, MI); John J. Oppenheimer, MD (Springfield, NJ); Charles Pollack, MD, MA (Phoenix, AZ); William W. Storms, MD (Colorado Springs, CO); and Carol Terregino, MD (Camberen, NJ).

References

20. Rodrigo G, Rodrigo C, Burschtin O. A meta-analysis of the effects of anticholinergics treatment for patients who do not demonstrate an adequate initial response to β-agonists, a substantial proportion of patients with asthma require additional treatment. The additional benefit of continued β-agonists and corticosteroids for patients with acute asthma who do not meet these initial response criteria is illustrated by the poor improvement in FEV1 observed for randomized patients receiving standardized therapy plus placebo (Figure 2). This study, if confirmed, suggests that montelukast may confer added benefit to current treatment options in the management of acute asthma.

References