

PHARMACOTHERAPY

The Efficacy and Tolerability of Intravenous Montelukast in Acute Asthma Exacerbations in Japanese Patients

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Objectives. In Japan, the Asthma Prevention and Management Guidelines recommend nebulized β -agonists, IV (intravenous) drip corticosteroids, as well as IV drip aminophylline for acute asthma treatment. However, current treatment for acute asthma provides inadequate benefit for some patients. We evaluated the efficacy and safety of IV montelukast added to standard therapy in Japanese patients with acute asthma exacerbations. **Methods.** This multicenter, randomized, double-blind, parallel-group study compared IV montelukast 7 mg, 14 mg, and placebo in Japanese patients with acute asthma exacerbations ($N = 242$). Fifteen- to sixty-five-year-old patients with acute asthma were treated with standard care during a screening period that lasted ≤ 60 minutes. Patients with FEV₁ (forced expiratory volume in 1 second) ≤ 70 predicted were randomly allocated to one of three treatment groups. The primary end point was the time-weighted average change in FEV₁ from baseline over 60 minutes [Δ FEV₁ (0–60 minutes)] after study drug administration. Secondary end points included the time-weighted average change in FEV₁ over 20, 40, and 120 minutes [Δ FEV₁ (0– T min)]. **Results.** IV montelukast 7 mg was significantly more effective than placebo for the time-weighted average Δ FEV₁ (0–60 minutes) [least squares (LS) mean 0.09 L vs. 0.01 L; $p < .05$]. IV montelukast 14 mg was also more effective than placebo (LS mean 0.17 L; $p < .001$). Similar improvements in time-weighted average [Δ FEV₁ (0– T min)] were seen at all time points (all $p < .05$). Both doses of IV montelukast demonstrated a significant increase in average Δ FEV₁ compared with placebo within 10 minutes of administration ($p < .001$ to $p < .01$). The tolerability of IV montelukast was similar to that of placebo. **Conclusion.** IV montelukast was significantly more effective than placebo in the improvement of Δ FEV₁ in Japanese patients, suggesting its role as an adjunctive therapy to existing guideline recommendations.

Keywords acute asthma, aminophylline, asthma exacerbation, intravenous montelukast, leukotriene receptor antagonist, randomized trial

INTRODUCTION

The primary goals of managing acute asthma exacerbations are correcting significant hypoxemia and rapid reversal of airflow obstruction (1). However, despite administering guideline-recommended therapy such as oxygen, β -agonists, systemic corticosteroids, and anticholinergics, up to 20% of adult patients treated in the emergency department for asthma require hospitalization (2). Moreover, airflow measures at presentation and 1 hour after treatment are the strongest predictors of hospitalization (3, 4).

In Japan, the Asthma Prevention and Management Guidelines for acute asthma recommend IV drip aminophylline in addition to interventions recommended by other guidelines (5). One study showed that IV drip aminophylline had significant effects on peak expiratory flow, forced expiratory volume in 1 second (FEV₁), and oxygen saturation in acute asthma, both when administered alone and when administered in combination with salbutamol (6). However, a review of 15 trials showed that IV drip

aminophylline administered along with β -agonists in adults with acute asthma did not result in additional bronchodilation, nor was there any significant effect on hospitalizations (7). In addition, the review found that IV drip aminophylline was associated with significantly more adverse experiences (AEs) of palpitations/arrhythmias and vomiting. Further, aminophylline and other xanthines have narrow therapeutic indices and hence require careful administration and clinical and laboratory monitoring. Given the benefits and risks of xanthines, their use in the acute setting is generally not recommended by other asthma treatment guidelines (1, 8). Thus, there is still a substantial need for new, safe, and effective therapies to improve outcomes in acute asthma exacerbations.

Oral montelukast has well-established efficacy and safety in chronic asthma (9). In clinical studies, intravenous (IV) montelukast significantly increased FEV₁ within 10 minutes compared with placebo in adults with acute asthma exacerbations (10, 11). IV montelukast was generally well tolerated, with no significant differences compared with placebo for the incidences of AEs.

IV montelukast 3 mg, 7 mg, and 18 mg were shown to be generally well tolerated in healthy Japanese subjects in a Phase I study, and AUC_{0–24} (area under the curve over

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24 hours) of montelukast 7 mg was similar to that for the oral 10-mg formulation (unpublished, data on file). However, its efficacy in acute asthma in the Japanese population has not been evaluated. The purpose of this trial was to assess the efficacy and tolerability of IV montelukast in Japanese patients with acute asthma exacerbations.

METHODS

Patients

All patients provided written informed consent prior to any study procedures. Consent from a parent or legal guardian was also obtained for patients who were 15–19 years old. The protocol and informed consent form were approved by the appropriate institutional review board, and the study was performed in accordance with the principles of Good Clinical Practices.

Fifteen- to sixty-five-year-old men and nonpregnant women with $FEV_1 \leq 70\%$ predicted, with at least 1-year history of asthma, and who were able to perform reproducible spirometry were considered eligible. Patients older than 54 years were required to demonstrate FEV_1 reversibility $\geq 12\%$ and ≥ 200 mL after β -agonist inhalation documented within the previous 5 years in order to exclude patients with chronic obstructive pulmonary disease (COPD). Pertinent exclusion criteria during the screening period included the following: any other known or suspected acute or chronic cause pulmonary symptoms (e.g., COPD); life-threatening asthma (e.g., need for intubation); temperature $>38^\circ\text{C}$; interval of more than 60 minutes between screening and study drug administration; $\geq 20\%$ decrease in FEV_1 between two screening measurements; $FEV_1 < 30\%$ predicted or oxygen saturation $< 90\%$ during screening; corticosteroids (other than a patient's usual daily dose) within 6 hours of screening; any antiasthma therapies other than approved therapies during screening; leukotriene receptor antagonist use within 8 hours of screening; and smoking history of > 15 pack-years.

Additional therapies excluded during the screening and treatment period included the following: leukotriene receptor antagonists; oral or parenteral corticosteroids (except for IV drip); inhaled corticosteroids; oral, parenteral, or transdermal β -agonists; long-acting β -agonists; inhaled cromolyn; xanthine derivatives or combinations (other than IV drip aminophylline); inhaled anticholinergics; halothane; helium–oxygen mixtures; magnesium salts; immunotherapy; subcutaneous epinephrine; and β -antagonists.

Study Design

This was a phase II/III randomized, double-blind, parallel-group study (Protocol 322; clinicaltrials.gov identifier NCT00229970) performed at 64 hospitals in Japan from 12 September 2005 to 23 October 2006 comparing IV montelukast 7 mg and 14 mg with placebo in patients with acute asthma exacerbations. Eligible patients entered a screening period lasting up to 60 minutes, during which

baseline spirometry was performed and standard therapy for acute asthma was initiated as needed, including oxygen and inhaled β -agonists (nebulized salbutamol 2.5 mg diluted in 2 mL saline administered over 5 minutes). If needed, patients could receive a second β -agonist administration after the first spirometry.

At the end of the screening period, patients were randomized to receive IV montelukast 7 mg, 14 mg, or placebo, each delivered as one manual IV bolus over 5 minutes. Patients were allowed to use oxygen, nebulized salbutamol 2.5 mg (administered no more frequently than every 15 minutes), and IV drip corticosteroids (hydrocortisone 200–500 mg or methylprednisolone 40–125 mg), each administered after spirometry at 20 minutes after study drug administration. IV drip aminophylline (250 mg) was administered after spirometry 60 minutes after study drug administration and as needed thereafter. Patients were observed for 120 minutes after study drug administration or until discontinuation, at which point patients were discharged or admitted for hospitalization. Follow-up by hospital visit or telephone call 14 days after completion was conducted to assess AEs.

Blinding was achieved using matching placebo and numbered containers. Drug reconstitution was performed by site staff who had no direct contact with patients. Study drug was administered using foil-wrapped syringes. Allocation was performed using sequential numbers according to a randomized table using permuted block randomization in blocks of six patients (two patients per treatment group). The code was broken after all data were collected and analyzed.

Spirometry

A standard spirometer was provided (ndd EasyOne, ndd Medical Technologies, Andover, MA). Spirometry was performed according to the American Thoracic Society reproducibility criteria (12), defined as the best two acceptable maneuvers with FEV_1 and forced vital capacity that do not vary by more than 200 mL. Because reproducibility in patients with acute asthma exacerbations may be difficult to achieve, the highest FEV_1 of three maneuvers was considered the best. Spirometry was performed at screening (baseline), at 10, 20, 40, 60, and 120 minutes after study drug administration, or at study discontinuation. The highest FEV_1 was determined from at least two, and preferably three, acceptable maneuvers.

Efficacy End Points

The primary efficacy end point was the time-weighted average change in FEV_1 from baseline over 60 minutes [average ΔFEV_1 (0–60 minutes)] after study drug administration. Secondary end points included the following: (i) average $\% \Delta FEV_1$ (0–60 minutes) after study drug administration; (ii) the time-weighted average ΔFEV_1 (0– T minutes) and the time-weighted average $\% \Delta FEV_1$ (0– T minutes), where T is the time from administration to 20 (0–20), 40 (0–40), and 120 (0–120) minutes after study drug administration; (iii) ΔFEV_1 and $\% \Delta FEV_1$ (T minutes), where T are time points 10, 20, 40, 60, and 120

minutes after study drug administration; (iv) the percentage of patients receiving IV corticosteroids and/or IV aminophylline during the treatment period; (v) the number of inhaled β -agonist doses during the treatment period; and (vi) patient and physician global evaluation 120 minutes after study drug administration, each scored on a seven-point scale (much improved, improved, slightly improved, no change, slightly worse, worse, and much worse). The difference in efficacy between the two montelukast doses was an additional end point.

Tolerability End Points

Tolerability was assessed through vital signs and AEs, including total clinical AEs, drug-related AEs as determined by investigators, serious AEs, and AEs leading to study discontinuation.

Statistical Methods

The primary hypothesis was that ΔFEV_1 (0–60 minutes) for IV montelukast 7 mg would be superior to that for placebo. The primary analysis was based on the Full Analysis Set (FAS) population, which included all patients who received study drug and who had available data at screening and during the treatment period. A per-protocol analysis including all patients without major protocol violations was performed to confirm the results. The primary efficacy analysis was carried out using an analysis of covariance (ANCOVA) model with treatment group as a factor and baseline FEV_1 as a cofactor to estimate the least squares (LS) mean change from baseline for each treatment group and between-treatment differences and the associated 95% confidence intervals (CI). Missing data were not imputed. Prespecified subgroup analyses for the primary end point included gender (male, female), age (≤ 55 , > 55 years), baseline FEV_1 ($\leq$ median, $>$ median), baseline $FEV_1\%$ predicted

($\leq 50\%$, $> 50\%$), baseline oxygen saturation ($\leq$ median, $>$ median), baseline respiration rate ($\leq$ median, $>$ median), and prior medication (leukotriene antagonists, oral corticosteroids, and oral xanthines) within 12 hours or 28 days of screening (yes, no).

Tolerability was assessed in all patients who received the study drug. AEs were estimated using Fisher's exact test, and between-group differences in AEs were estimated using Wilson's score.

Assuming a difference in average ΔFEV_1 (0–60 minutes) of 0.18 L between the montelukast 7 mg group and placebo and a standard deviation of 0.37 L, a sample size of 75 patients per group would have 85% power to detect a difference of 0.18 L between montelukast 7 mg and placebo at $\alpha = 0.05$ (two-tailed). This sample size is based on the results of a pilot study with non-Japanese acute asthma comparing montelukast 7 mg, 14 mg, and placebo (10).

Because there was a single primary hypothesis and a single comparison (IV montelukast 7 mg vs. placebo), no adjustment for multiplicity was required. There were no formal comparisons between montelukast doses; thus, no step-down procedures were performed. No adjustment for multiplicity was performed for the secondary analyses. Results should be interpreted accordingly.

RESULTS

Patients

Figure 1 shows patient disposition throughout the study. A total of 242 patients were randomized, of which 225 entered the treatment period, and these 225 patients completed the study and were included in the FAS population. The mean age was approximately 41 years, and there were approximately equal numbers of men and women

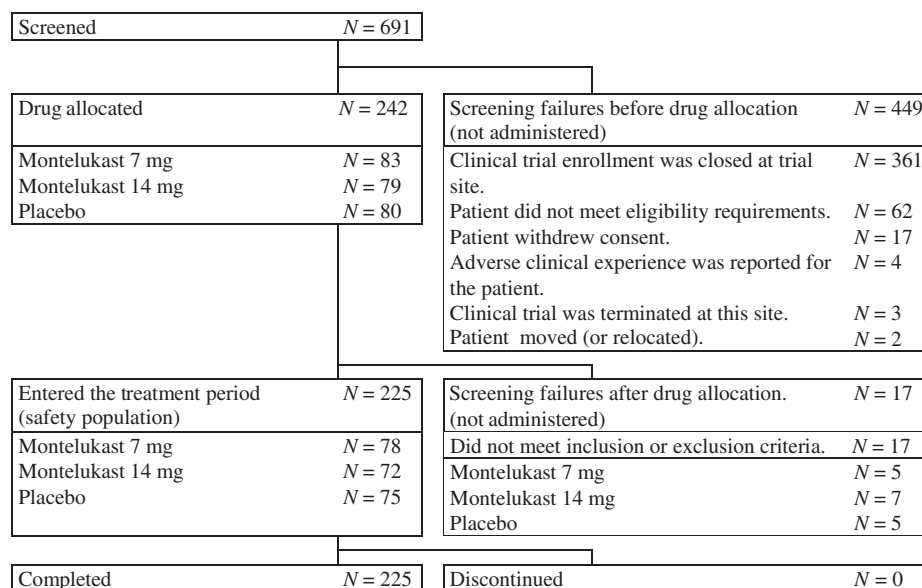


FIGURE 1.—Patient disposition.

TABLE 1.—Baseline patient characteristics.

	Montelukast 7 mg (N = 78)	Montelukast 14 mg (N = 72)	Placebo (N = 75)
Gender			
Male	37 (47.4)	38 (52.8)	39 (52.0)
Female	41 (52.6)	34 (47.2)	36 (48.0)
Age (years)			
Mean	40.5 (12.5)	41.5 (13.1)	42.3 (12.5)
15 to <55	67 (85.9)	60 (83.3)	60 (80.0)
55 to <66	11 (14.1)	12 (16.7)	15 (20.0)
Asthma attack severity (mild, moderate, severe, and serious)			
Mild	54 (69.2)	44 (61.1)	56 (74.7)
Moderate	23 (29.5)	28 (38.9)	19 (25.3)
Severe	1 (1.3)	0 (0.0)	0 (0.0)
Serious	0 (0.0)	0 (0.0)	0 (0.0)
Medication use within 12 hours of screening			
Leukotriene receptor antagonists			
No	74 (94.9)	69 (95.8)	74 (98.7)
Yes	4 (5.1)	3 (4.2)	1 (1.3)
Oral corticosteroids			
No	72 (92.3)	70 (97.2)	71 (94.7)
Yes	6 (7.7)	2 (2.8)	4 (5.3)
Xanthine derivatives			
No	59 (75.6)	56 (77.8)	62 (82.7)
Yes	19 (24.4)	16 (22.2)	13 (17.3)
Respiration rate (breaths/minute), mean (SD)	19.6 (5.2)	19.7 (4.6)	20.1 (4.6)
Baseline FEV ₁ (% predicted), mean (SD)	53.7 (11.4)	50.5 (12.6)	55.0 (10.9)
Baseline FEV ₁ (L), mean (SD)	1.67 (0.55)	1.62 (0.59)	1.76 (0.61)
Peripheral oxygen saturation (%), mean (SD)	95.2 (2.1)	95.4 (2.1)	95.2 (1.9)
Smoking			
Absence	51 (65.4)	49 (68.1)	47 (62.7)
Presence	27 (34.6)	23 (31.9)	28 (37.3)

Notes: FEV₁, forced expiratory volume in 1 second; SD, standard deviation.

Unless otherwise mentioned, all values represent *n* (%).

Asthma attack severity (mild, moderate, severe, and serious) was classified by the investigators based on Japanese Guidelines for the Diagnosis and Management of Asthma (2003).

(Table 1). Overall baseline demographics and asthma measures were similar across treatment groups.

Efficacy

For the primary end point of change from baseline in the time-weighted average Δ FEV₁ (0–60 minutes), montelukast 7 mg was superior to placebo (LS mean 0.09 L vs. 0.01 L, respectively; $p < .05$) (Figure 2, Table 2). Montelukast 14 mg was also superior to placebo for average Δ FEV₁ (0–60 minutes) (0.17 L; $p < .001$). Both montelukast doses were superior to placebo in the per-protocol analysis of the primary end point ($p < .05$ to $p = .001$; data not shown).

Compared with placebo, both montelukast doses were superior in the time-weighted average % Δ FEV₁ (0–60 minutes) ($p < .001$ to $p < .05$) and all time-weighted average Δ FEV₁ (0–20, 0–40, and 0–120 minutes). The montelukast 7 mg group demonstrated a significant increase in average % Δ FEV₁ (0–20 minutes) and average % Δ FEV₁ (0–40 minutes) relative to the placebo group. The montelukast 14 mg group demonstrated a significant increase in all average % Δ FEV₁ (0–20, 0–40, and 0–120 minutes) relative to the placebo group (data not shown). Both montelukast doses demonstrated a significant increase in Δ FEV₁ compared with placebo within 10 minutes after the completion of administration ($p < .001$ to $p < .01$). Montelukast 14 mg was superior through the full 120-minute study period, and montelukast 7 mg was superior to placebo through 40 minutes, but continued to be numerically better than placebo for the remainder of the study (Figure 3).

Additional statistical significance for montelukast relative to placebo included the number of β -agonist doses for montelukast 14 mg ($p < .01$) and patient and physician global evaluation for montelukast 7 mg ($p < .05$ for both) (Table 2). There were no differences between montelukast

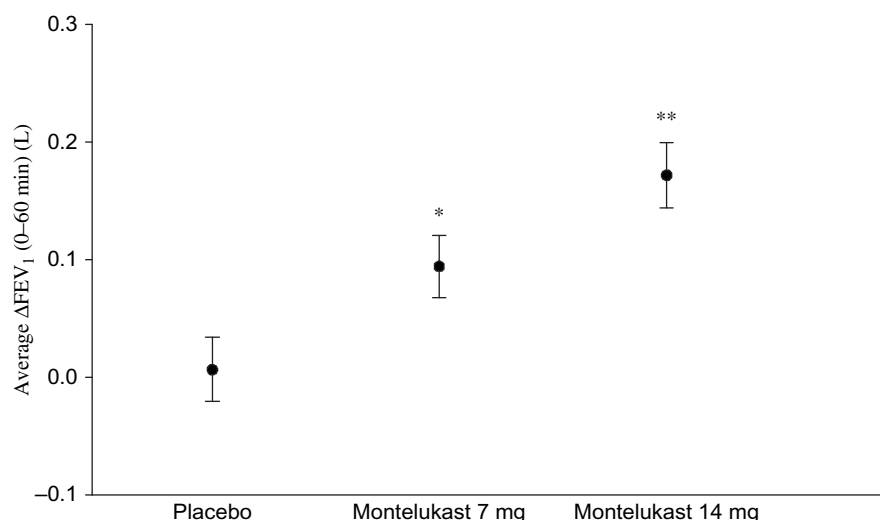


FIGURE 2.—Primary efficacy end point: average Δ FEV₁ (0–60 minutes). * $p < .05$ vs. placebo; ** $p < .001$ vs. placebo and $p < .05$ vs. montelukast 7 mg. Values are least squares means $\pm$ standard error.

TABLE 2.—Primary and key secondary efficacy end points.

End point	Montelukast 7 mg N = 78	Montelukast 14 mg N = 72	Placebo N = 75
Primary end point: average Δ FEV ₁ (0–60 min), L	0.09 (0.04, 0.15)*	0.17 (0.12, 0.23)***	0.01 (–0.05, 0.06)
Average % Δ FEV ₁ (0–60 min) (%)	5.56 (2.44, 8.69)*	11.32 (8.06, 14.57)***	0.91 (–2.28, 4.10)
Average Δ FEV ₁ (0–20 min) (L)	0.08 (0.04, 0.13)**	0.15 (0.10, 0.20)***,****	0.00 (–0.05, 0.04)
Average Δ FEV ₁ (0–40 min) (L)	0.09 (0.04, 0.14)**	0.16 (0.11, 0.22)***,****	0.00 (–0.05, 0.05)
Average Δ FEV ₁ (0–120 min) (L)	0.09 (0.03, 0.15)*	0.18 (0.11, 0.24)***,****	0.00 (–0.06, 0.06)
Patients receiving corticosteroids or aminophylline (%)	44.9 (33.6, 56.6)	40.3 (28.9, 52.5)	45.3 (33.8, 57.3)
β -agonist doses per patient, median	0 (0.00, 0.00)	0 (0.00, 0.00)**	0 (0.00, 0.00)
Patients reporting “much improved” or “improved” global evaluation (%)	61.5 (49.8, 72.3)*	54.2 (42.0, 66.0)	44.0 (32.5, 55.9)
Physicians reporting “much improved” or “improved” global evaluation (%)	48.7 (37.2, 60.3)*	44.4 (32.7, 56.6)	29.3 (19.4, 41.0)

Notes: Results are presented as values (mean, median, or percent) and associated 95% CI.

* $p < .05$ vs. placebo.

** $p < .01$ vs. placebo.

*** $p < .001$ vs. placebo.

**** $p < .05$ vs. montelukast 7 mg.

FEV₁: forced expiratory volume in 1 second;

Patients' and Physicians' global evaluations were scored on an identical seven-point scale: 1. Very much improved, 2. Moderately improved, 3. A little improved, 4. Unchanged, 5. A little worse, 6. Moderately worse, 7. Very much worse.

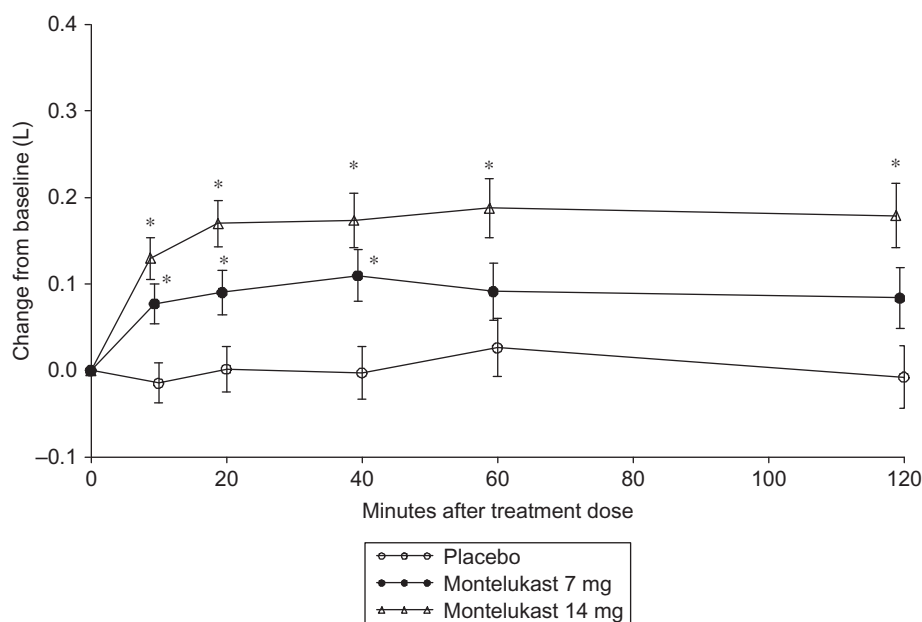


FIGURE 3.—Changes from baseline in Δ FEV₁ over 120 minutes after study drug administration. * $p < .05$ vs. placebo. Values are least squares means $\pm$ standard error.

(either dose) compared with placebo for the percentage of patients receiving corticosteroids and/or aminophylline rescue during the treatment period.

Montelukast 14 mg was significantly more effective than montelukast 7 mg for the time-weighted average Δ FEV₁ beyond 20 minutes.

Prespecified Subgroup Analysis for Primary End Point

The results of subgroup analyses for the primary end point average Δ FEV₁ (0–60 minutes) by different background factors are shown in Table 3. In the subgroup of patients with a predicted baseline FEV₁ of $>50\%$, average Δ FEV₁ (0–60 minutes) in the montelukast 7 mg and 14 mg groups was comparable, but in the subgroup of patients with an

estimated FEV₁ of $\leq 50\%$, the response in the 14 mg group was numerically higher than in the 7 mg group. Similar results were observed in the subgroup of patients with a measured baseline FEV₁ $\leq$ median [1.57 L]. No major difference was seen among other subgroups.

Tolerability

No significant differences were observed in the incidences of clinical AEs among the three treatment groups, and no patients discontinued due to an AE (Table 4). There were 10 drug-related AEs in nine patients. There were six AEs in the montelukast 7 mg group (palpitations, diarrhea, gastritis, nausea, blood pressure increased, body temperature increased, and somnolence) and three AEs in the placebo

TABLE 3.—Subgroup analysis of average ΔFEV_1 (0–60 minutes).

Subgroup	Treatment group	N	Change from baseline (L)			
			Mean	SD	LS mean	95% CI of difference with placebo
Baseline FEV ₁ : predicted values						
≤50%	Placebo	26	0.03	0.11	0.04	–
	Montelukast 7 mg	28	0.11	0.27	0.10	(–0.08, 0.20)
	Montelukast 14 mg	38	0.23	0.32	0.22	(0.05, 0.31)
>50%	Placebo	49	0.00	0.19	–0.01	–
	Montelukast 7 mg	50	0.09	0.22	0.09	(0.01, 0.18)
	Montelukast 14 mg	34	0.11	0.23	0.11	(0.02, 0.21)
Baseline FEV ₁ : measured values						
≤Median (1.57 L)	Placebo	33	0.03	0.09	0.03	–
	Montelukast 7 mg	41	0.05	0.13	0.04	(–0.07, 0.09)
	Montelukast 14 mg	39	0.16	0.25	0.17	(0.05, 0.21)
>Median (1.57 L)	Placebo	42	–0.01	0.21	–0.01	–
	Montelukast 7 mg	37	0.15	0.31	0.15	(0.03, 0.28)
	Montelukast 14 mg	33	0.18	0.33	0.18	(0.06, 0.32)

TABLE 4.—Summary of clinical AEs.

	Montelukast 7 mg (N = 78)	Montelukast 14 mg (N = 72)	Placebo (N = 75)
With any AEs	21 (26.9)	14 (19.4)	19 (25.3)
With drug-related ^a AEs	6 (7.7)	0 (0.0)	3 (4.0)
With serious AEs	2 (2.6)	4 (5.6)	4 (5.3)
Discontinued due to AE	0 (0.0)	0 (0.0)	0 (0.0)
With serious drug-related AEs	1 (1.3)	0 (0.0)	0 (0.0)
Who died	0 (0.0)	0 (0.0)	0 (0.0)

Notes: ^aDetermined by the investigator to be possibly, probably, or definitely drug related.

All values represent *n* (%).

A patient may be included in one or more categories.

group (blood pressure decreased, rash, and hot flush). One patient in the montelukast 7 mg group was hospitalized for gastritis. This event occurred on the day of study drug administration; the patient was hospitalized on day 2 and recovered on day 8.

There were 10 serious AEs. Two patients in the montelukast 7 mg group were hospitalized: one for gastritis and one for asthma. Four patients in the montelukast 14 mg group were hospitalized due to asthma. Four patients in placebo group were hospitalized: one for acute tonsillitis, one for abdominal pain, and two for asthma. All these patients recovered within 19 days.

There were eight drug-related laboratory AEs in seven patients. Five AEs occurred in the montelukast 7 mg group (white blood cell count increased, blood bilirubin increased, blood potassium decreased, glucose urine present, and urobilin urine present), and three AEs occurred in the placebo group (white blood cell count increased, blood sodium decreased, and glucose urine present). There were no clinically meaningful differences in incidence among three treatment groups and no dose-dependent relationships.

DISCUSSION

Asthma is characterized by exacerbations that may be life-threatening. These exacerbations are induced by triggers

such as viruses, aspirin, allergens, and physical exertions that cause the release of inflammatory mediators, including leukotrienes. Although current standard treatments for acute asthma—including supplemental oxygen, β_2 -agonists, corticosteroids, and anticholinergics (for severe exacerbations)—are effective in most patients, they are inadequate in a significant proportion, leading to hospitalization. Therefore, there is a need for new treatment options that provide benefits beyond the current standard treatments.

Montelukast is a potent leukotriene receptor antagonist that, when taken orally, provides benefit in asthma by decreasing airway inflammation and reversing bronchoconstriction. Camargo et al. (10) found that the addition of IV montelukast to standard care produced a rapid improvement in FEV₁ in acute asthma. Such a role for montelukast in acute asthma is supported by the observation of increased urinary leukotriene E₄ levels in patients with acute asthma (13).

The Japanese asthma guidelines recommend IV drip aminophylline as adjunctive therapy to β -agonists for acute asthma exacerbations. However, it is usually administered for less than 60 minutes, although there were safety concerns with xanthines. A previous open-label, exploratory study demonstrated comparable and significant improvements in the primary efficacy end point of

average ΔFEV_1 (0–60 minutes) with IV montelukast 7 mg (0.07 L), 14 mg (0.05 L), and aminophylline (0.06 L). The comparable efficacy between montelukast and aminophylline and the favorable tolerability profile of montelukast suggest a role for montelukast as an adjunctive therapy for acute asthma exacerbations.

The purpose of this study was to evaluate the efficacy and tolerability of IV montelukast added to standard therapy in acute asthma exacerbations in Japanese patients. We found that IV montelukast 7 mg and 14 mg were significantly more effective than placebo for the primary end point of the average ΔFEV_1 (0–60 minutes) (Figure 3). Importantly, a significant increase in ΔFEV_1 was seen with both montelukast doses within 10 minutes compared with placebo that was sustained for the entire 120-minute study period for montelukast 14 mg and through 40 minutes for montelukast 7 mg (Figure 3).

Both doses of montelukast were significantly more effective than placebo for most secondary end points, with the exception of the percentage of patients receiving corticosteroids or aminophylline, for which there were no significant differences between either dose of montelukast and placebo. Montelukast 14 mg was significantly more effective than montelukast 7 mg for average ΔFEV_1 beyond 20 minutes.

All treatments were generally well-tolerated, and the incidences of AEs with montelukast were similar to those with placebo.

Overall these results are highly consistent with earlier studies of IV montelukast in acute asthma. Camargo et al. (10) conducted a study in the US ($N = 201$) similar to the present study, in which both IV montelukast 7 mg and 14 mg were superior to placebo for the primary end point of ΔFEV_1 (0–20 minutes). There were no additional benefits observed for the 14 mg dose over the 7 mg dose. When the montelukast doses were pooled, montelukast was superior to placebo for corticosteroid use and the percentage of patients receiving >2 doses of β -agonist during treatment period. There was no difference from placebo in hospitalizations.

A more recent, large multinational study by Camargo et al. (11) ($N = 583$) showed that IV montelukast 7 mg was superior to placebo for the primary end point of ΔFEV_1 (0–60 minutes) (LS mean 0.32 L vs. 0.22 L; $p < .001$ vs. placebo). Although the absolute effect of montelukast 7 mg was substantially larger in that study than in the present study (0.32 vs. 0.09 L), the change with placebo was also substantially larger (0.22 vs. 0.01). The difference in absolute effect is likely attributable to the screening requirement of $FEV_1 \leq 50\%$ predicted in the previous study compared with $\leq 70\%$ predicted for this study. Unsurprisingly, therefore, patients in the study by Camargo et al. (11) had substantially lower baseline FEV_1 (mean 1.25 L) compared with those in this study (mean 1.68) and thus had greater room for improvement. Importantly, the placebo-adjusted changes are highly consistent between the two studies (0.10 L vs. 0.09 L), suggesting that the efficacy in the Japanese population is similar to that for a broader population.

Prespecified analyses suggested that in the subgroup of patients with $FEV_1 > 50\%$ predicted, average ΔFEV_1 (0–60 minutes) in the montelukast 7 mg and 14 mg groups was comparable, but in the subgroup of patients with $FEV_1 \leq 50\%$ predicted, the response in the 14 mg group was greater than in the 7 mg group. Similar results were observed in the subgroup of patients with a measured baseline $FEV_1 \leq$ median [1.57 L]. The subgroup results, although preliminary and thus needing confirmation, suggest that there may be additional benefit observed for the 14 mg dose over the 7 mg dose in severe acute asthma patients.

Although the percentage of patients with treatment failure (defined as hospitalization or lack of decision to discharge by 3 hours postadministration) was evaluated as the key secondary end point in the previous study, we did not collect information regarding treatment failure in this study. At the time of this study, there were no clear, uniform hospitalization criteria in the Japanese asthma guidelines. Because the decision to admit or discharge patients with asthma is highly variable, we did not assess treatment failure.

In conclusion, IV montelukast provides rapid, sustained bronchodilation in Japanese patients with acute asthma exacerbations. The efficacy and tolerability profile support the clinical utility of IV montelukast as an alternative adjunctive therapy in managing acute asthma.

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