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Original Article

Early control treatment with montelukast in preschool children with asthma: A randomized controlled trial

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GINA, Global Initiative for Asthma;

EPR-3, Expert Panel Reports 3;

JGCA, Japanese guideline for childhood

asthma; ICS, inhaled corticosteroid;

SpO₂, oxygen saturation of peripheral

artery; CI, confidence interval

ABSTRACT

Background: While Japanese guideline recommends initial control treatment for preschool children with asthma symptoms more than once a month, Western guidelines do not. To determine whether control treatment with montelukast was more effective than as-needed β_2 -agonists in this population, we conducted a randomized controlled trial.

Methods: Eligible patients were children aged 1–5 years who had asthma symptoms more than once a month but less than once a week. Patients were randomly assigned in a 1:1 ratio to receive montelukast 4 mg daily for 48 weeks or as-needed β_2 -agonists. The primary endpoint was the number of acute asthma exacerbations before starting step-up treatment with inhaled corticosteroids. This study is registered with the University Hospital Medical Information Network clinical trials registry, number UMIN000002219.

Results: From September 2009 to November 2012, 93 patients (47 in the montelukast group and 46 in the no-controller group) were enrolled into the study. All patients were included in the analysis. During the study, 13 patients (28%) in the montelukast group and 23 patients (50%) in the no-controller group had acute exacerbations with the mean numbers of 0.9 and 1.9/year, respectively ($P = 0.027$). In addition, 10 (21%) and 19 (41%) patients received step-up treatment, respectively. Cumulative incidence of step-up treatment was significantly lower in the montelukast group (hazard ratio 0.45, 95% confidence interval 0.21 to 0.92; $P = 0.033$).

Conclusions: Montelukast is an effective control treatment for preschool children who had asthma symptoms more than once a month but less than once a week.

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Introduction

Despite advances in the management of asthma, its optimal treatment strategy in early childhood remains uncertain. Although current guidelines recommend initial control treatment for children with mild persistent asthma, their classifications of severity are different. For example, if patients have asthma symptoms more

than once a week but less than once a day, they are classified into mild persistent asthma by the Global Initiative for Asthma (GINA) report entitled “Global strategy for asthma management and prevention”.¹ The National Asthma Education and Prevention Program’s Expert Panel Reports 3 (EPR-3) also adopts a similar classification.² In contrast, Japanese guideline for childhood asthma (JGCA) defines the term as symptoms occurring more than once a month but less than once a week.³ As a result, JGCA recommends starting control treatment in earlier disease stage.

In addition, JGCA includes leukotriene antagonists in controller medications,³ whereas the GINA report and EPR-3 recommend

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inhaled corticosteroids (ICSs) as the most effective controller medication.^{1,2} JGCA also recommends ICSs for children who have asthma symptoms more than once a week, as well as the GINA report and EPR-3. However, JGCA recommends leukotriene antagonists and low-dose ICSs for those with symptoms more than once a month in contrast to the other guidelines. This JGCA's recommendation has arisen from the results of previous randomized controlled trials showing that the efficacy of leukotriene antagonists was similar to that of ICSs.^{4,5}

In treating preschool children, the treatment strategy recommended by JGCA has some potential advantages. First, starting control treatment in early disease stage may help prevent acute exacerbations and disease progression. Second, anti-inflammatory agents other than ICSs may derive favorable outcomes in early stage. Although the benefits of ICSs in patients with persistent asthma have been well established,^{6,7} their early use in preschool children had no effect on the natural history of asthma.^{8–10} Moreover, the use of ICSs in childhood—especially in early childhood—has been reported to be associated with a reduction in linear growth.^{11,12} Third, treatment with oral anti-inflammatory drugs may lead to favorable patients' adherence because slow inhalation is difficult in young children. A face mask allows young children to use metered-dose inhaler, but daily use of a face mask is cumbersome. Considering these, it is worthwhile to investigate the benefits of control treatment with an oral anti-inflammatory drug in early disease stage.

Montelukast is a cysteinyl leukotriene 1 receptor antagonist. A previous clinical trial has shown that montelukast significantly reduced the rate of asthma exacerbations in children who had a history of intermittent asthma symptoms resulting from an upper respiratory infection.¹³ However, this trial included only those with viral-induced asthma, and it was uncertain whether children with intermittent asthma should be treated daily with montelukast. Accordingly, we conducted a randomized controlled trial to determine whether montelukast was superior to as-needed β_2 -agonists in treating preschool children who had asthma symptoms less than once a week.

Methods

Study setting and ethical considerations

This multicenter, open-label, randomized controlled trial was conducted between September 2009 and October 2013 at 14 institutions in Japan. Its protocol was centrally reviewed and approved by the institutional review board of Mie National Hospital. All patients' guardians provided written informed consent.

Patients

Eligible patients were children aged 1–5 years who had mild persistent asthma according to the classification by JGCA. For children with 2–5 years of age, those who had episodes of asthma symptoms more than once a month but less than once a week were eligible for the study. In addition to this criterion, children aged 1 year had to experience at least 3 episodes of expiratory wheezing and had to meet both of the following categories: A) expiratory wheezing, exertional dyspnea, or oxygen saturation of peripheral artery (SpO₂) was improved by inhaled short-acting β_2 -agonist; and B) the patient had a physician's diagnosis of atopic dermatitis, evidence of food allergy, or parental history of asthma. We added these criteria because accurate diagnosis of asthma in younger children was challenging.

Patients were excluded from the study if they had received either of the following treatment within 6 months before the study:

oral anti-allergic medicine including leukotriene antagonists, inhaled or oral corticosteroids, sustained-release theophylline, or long-acting β_2 -agonists.

Treatment

Patients were randomly assigned in a 1:1 ratio to receive montelukast or as-needed β_2 -agonists using a minimization method with the stratification factors of age (1 year vs. 2–5 years), sex, with or without atopic dermatitis, and with or without parental history of asthma. Allocation sequence was created using the computer by the study office (Nouvelle Place, Tokyo, Japan). When a patient was considered to be eligible for the study, the investigator contacted the study office through telephone. The study office confirmed the eligibility and notified the study drug to be administered. The study office was not involved in the patient enrollment.

During the treatment period of 48 weeks, patients in the montelukast group received one packet of 4-mg oral granules once a day. If patients reached the age of 6, they received 5-mg chewable tablet once a day. In the no-controller group, patients inhaled β_2 -agonist as an as-needed reliever medication according to the GINA report.

In both groups, concomitant use of oral anti-allergic drug, sustained-release theophylline, long-acting β_2 -agonist, or oral corticosteroid was prohibited. As-needed treatment with short-acting β_2 -agonist was allowed if patients had asthma symptoms. Patients started control treatment with ICS if they reported expiratory wheezing and disturbed nocturnal sleep (or the combination of expiratory wheezing and dyspnea) in more than 5 days during 4 weeks. ICS was discontinued if the investigators decided to start step-down treatment.

Outcomes

At the beginning of the study, medical histories were obtained from all patients. During the treatment period, patients visited the institutions every 4 weeks. At each visit, the investigators examined patients' symptoms and signs and determined whether they needed step-up treatment or not. They also performed laboratory tests at 24-week intervals.

Patients' guardians were given a questionnaire booklet. If patients had an acute asthma exacerbation, their guardians asked the physicians who treated the patients to record the following in the booklet: date of onset; name of the institutions where the patients were treated; severity of asthma symptoms; measurements of SpO₂; names and doses of the medications used; and with/without the need for hospitalization. If patients were treated in the study institutions, physicians other than the investigators recorded them in the booklet.

The primary endpoint was the number of acute asthma exacerbations before starting step-up treatment with ICS. After the treatment period was over, the study office collected the booklets and adjudicated the number of acute asthma exacerbations. For each recorded exacerbation, the study office determined its grade. When the grade was moderate or higher, the study office also determined whether it was acute exacerbation or not according to the protocol. In the protocol, acute exacerbation was defined as severe wheeze with dyspnea or hypoxemia of SpO₂ <92% that required systemic corticosteroids or hospitalization. The secondary endpoints included the time to the first onset of acute asthma exacerbation, time to the start of step-up treatment with ICS and symptom-free days. Sensitization status was examined by measuring specific IgE values to house dust mite, dog dander, cat dander, Japanese cedar pollen, milk and egg white using the

ImmunoCAP® specific IgE (Phadia AB, Uppsala, Sweden). Specific IgE value >0.35 kU_A/L was considered positive sensitization.

Statistical considerations

A sample size of 100 patients (50 in each group) was determined on the basis of feasibility, because available data for calculating the sample size were limited.

The primary and secondary endpoints were analyzed according to the intention-to-treat principle. The Mann–Whitney *U* test was used to compare the number of acute asthma exacerbations between the treatment groups. In addition, the log-rank test was used to compare the time to the first onset of acute asthma exacerbation and time to the start of step-up treatment with ICS. All data were analyzed with the use of GraphPad Prism 7 (GraphPad Software, CA, USA). All reported *P* values are two sided.

Results

Figure 1 shows the flow chart of the study patients. From September 2009 to November 2012, 93 patients (47 in the montelukast group and 46 in the no-controller group) were enrolled into the study. Of these, 1 patient in the no-controller group did not receive the allocated treatment because of prescription error and received montelukast for 48 weeks. Moreover, 9 patients did not complete the study because of lost to follow-up (4 in the montelukast group and 1 in the no-controller group), patient's decision (1 in the montelukast group), and asthma exacerbation (3 in the no-controller group). All patients were included in the analysis according to the treatment groups to which they were originally assigned.

The baseline characteristics were well balanced between the treatment groups (Table 1). The mean (standard deviation) ages were 2.3 (1.3) in the montelukast group and 2.7 (1.3) in the no-controller group. There were no differences in gender, age, anthropometric measurements and clinical features including sensitization. In both groups, nearly half patients had atopic dermatitis and about 80% were sensitized to common allergens.

Table 1
Baseline characteristics of the study patients.

	Montelukast (n = 47)	No-controller (n = 46)	<i>P</i> value
Boys (n, %)	22 (47)	16 (35)	0.293 [†]
Age [years, mean (SD)]	2.3 (1.3)	2.7 (1.3)	0.141 [‡]
Height [cm, mean (SD)]	89.6 (12.1)	91.4 (10.3)	0.442 [‡]
Weight [kg, mean (SD)]	13.5 (4.5)	12.9 (2.6)	0.435 [‡]
Clinical features			
Atopic dermatitis (n, %)	20 (43)	21 (46)	0.836 [†]
Parental history of asthma (n, %)	20 (43)	18 (39)	0.834 [†]
Sensitization (ImmunoCAP >0.35 kU _A /L)			
House dust mite (n, %)	24 (51)	17 (63)	0.297 [†]
Dog (n, %)	9 (19)	9 (20)	0.999 [†]
Cat (n, %)	5 (11)	6 (13)	0.759 [†]
Japanese cedar pollen (n, %)	13 (28)	20 (28)	0.999 [†]
Milk (n, %)	19 (40)	20 (43)	0.835 [†]
Egg white (n, %)	29 (62)	28 (61)	0.999 [†]
Any sensitization above (n, %)	36 (77)	38 (83)	0.608 [†]

n, number of the patients; SD, standard deviation.

Patient demographics and baseline clinical characteristics were balanced between study groups.

[†] Chi-square test.

[‡] *t* test.

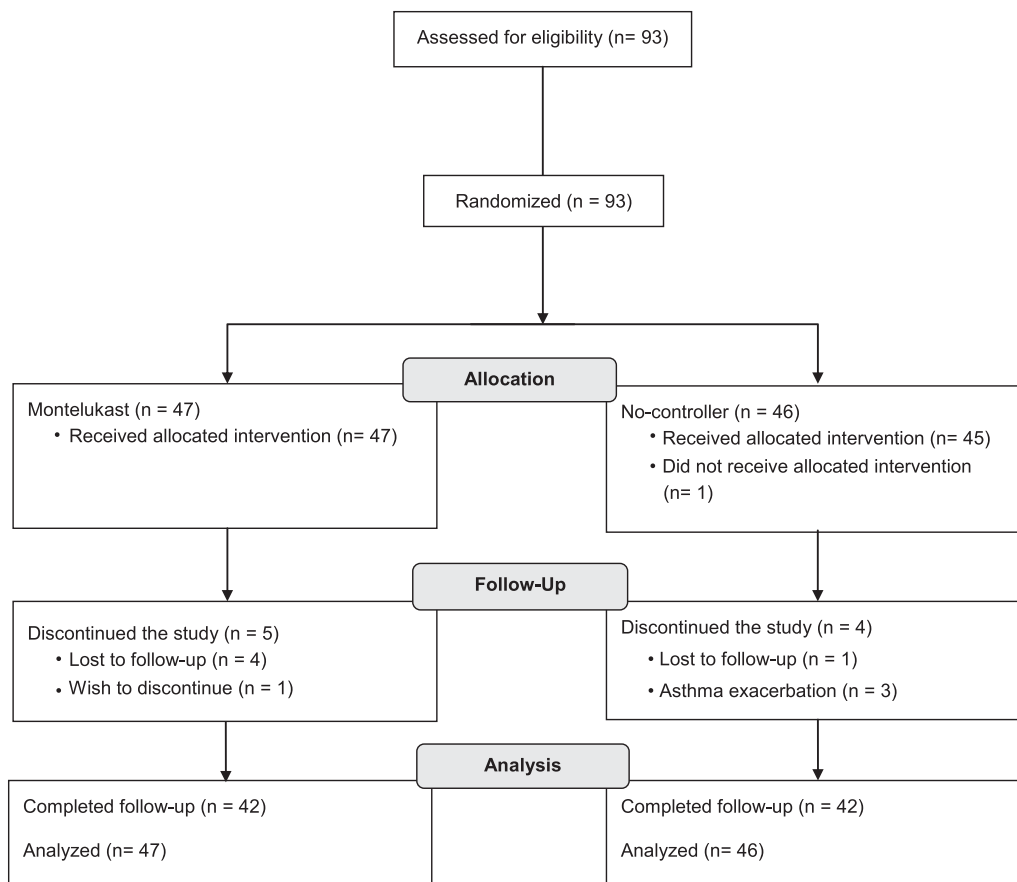


Fig. 1. Flow chart of the study patients.

During the study, 13 patients (28%) in the montelukast group and 23 patients (50%) in the no-controller group had acute asthma exacerbations with the mean numbers of 0.08/month (0.9/year) and 0.16/month (1.9/year), respectively (Fig. 2). No patient had an acute exacerbation that required the long-term (≥ 6 days) treatment with oral corticosteroid. Mean number of acute exacerbations was significantly lower in the montelukast group than in the no-controller group ($P = 0.027$). Cumulative incidence of acute exacerbations was significantly lower in the montelukast with the hazard ratio of 0.41 (95% confidence interval [CI] 0.20 to 0.72; $P = 0.004$; Fig. 3). In addition, 10 patients (21%) in the montelukast group and 19 (41%) in the no-controller group received step-up

treatment (Fig. 4). Cumulative incidence of step-up treatment was significantly lower in the montelukast group (hazard ratio 0.45, 95% CI 0.21 to 0.92; $P = 0.033$). Mean symptom-free days were around 95% throughout the study period and there was no difference between the groups (Supplementary Fig. 1). Days of beta-agonist use including inhaled, oral and percutaneous formulations in montelukast group were significantly lower than in no-controller group, 1.2 ± 2.6 and 3.6 ± 3.6 days per month, respectively (Fig. 5).

Table 2 summarizes the adverse events. During the treatment period, 4 patients (9%) in each group had at least 1 adverse event. Patients in the montelukast group reported upper respiratory infection, gastroenteritis, hand-foot-and-mouth disease, urticaria,

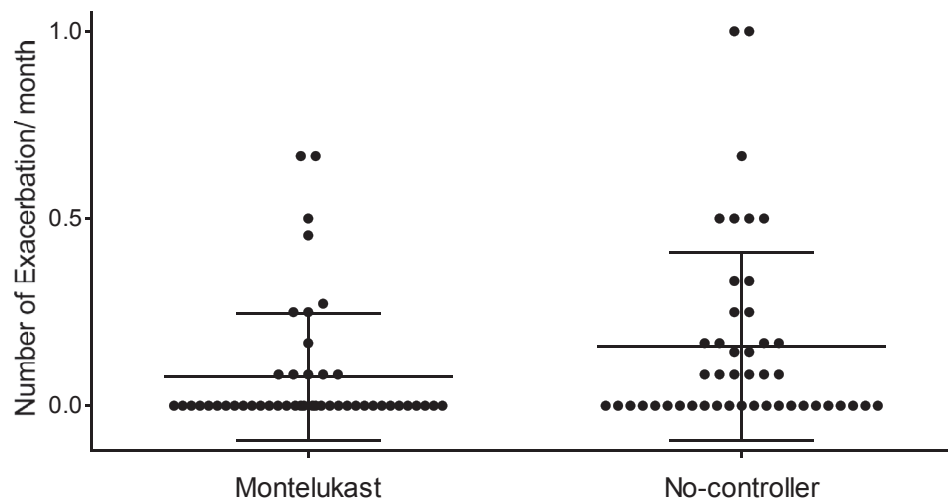


Fig. 2. Number of acute asthma exacerbations until starting step-up treatment in each patient. Each dot indicates the number of exacerbations per month in each patient randomized to the montelukast or no-controller group. Horizontal lines in each treatment group indicate the mean $\pm$ 1 standard deviation ($P = 0.027$, Mann–Whitney U test).

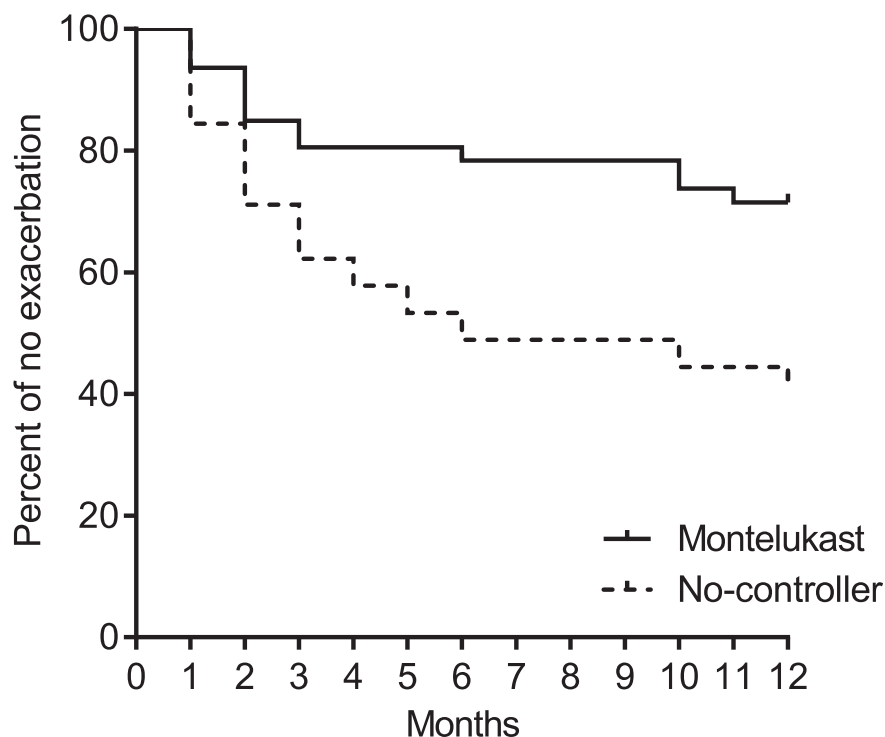


Fig. 3. Proportion of the patients who did not have acute asthma exacerbations throughout the study. Solid line indicates the Kaplan–Meier curve of the montelukast group and dotted line indicates that of the no-controller group. The time to the first onset of acute asthma exacerbation was compared between the treatment groups with the use of the log-rank test ($P = 0.004$).

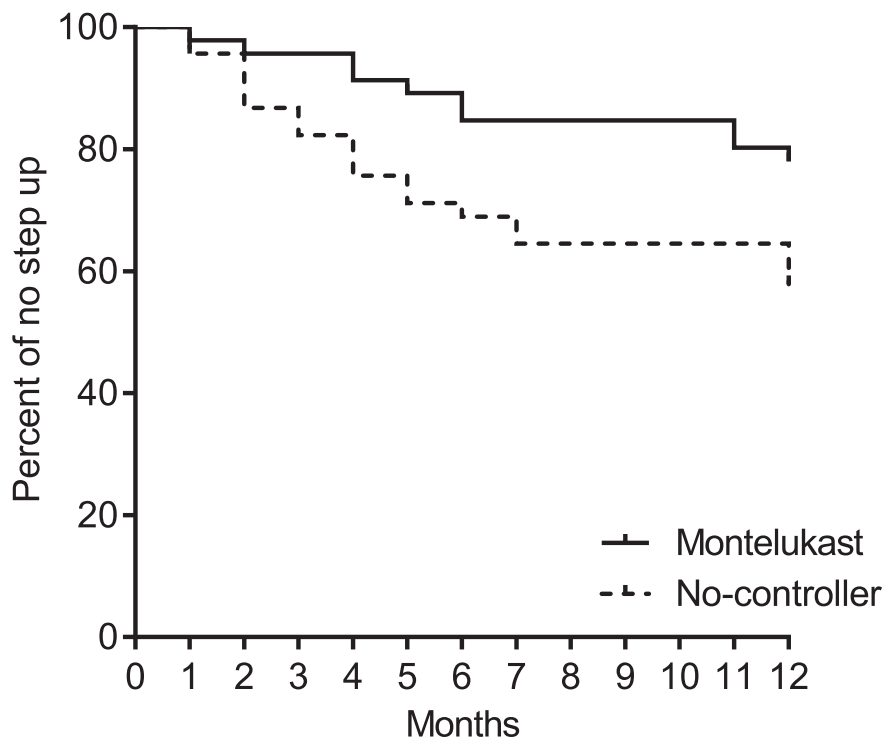


Fig. 4. Proportion of the patients who did not need step-up treatment with inhaled corticosteroids throughout the study. Solid line indicates the Kaplan–Meier curve of the montelukast group and dotted line indicates that of the no-controller group. The time to the start of step-up treatment was compared between the treatment groups with the use of the log-rank test ($P = 0.033$).

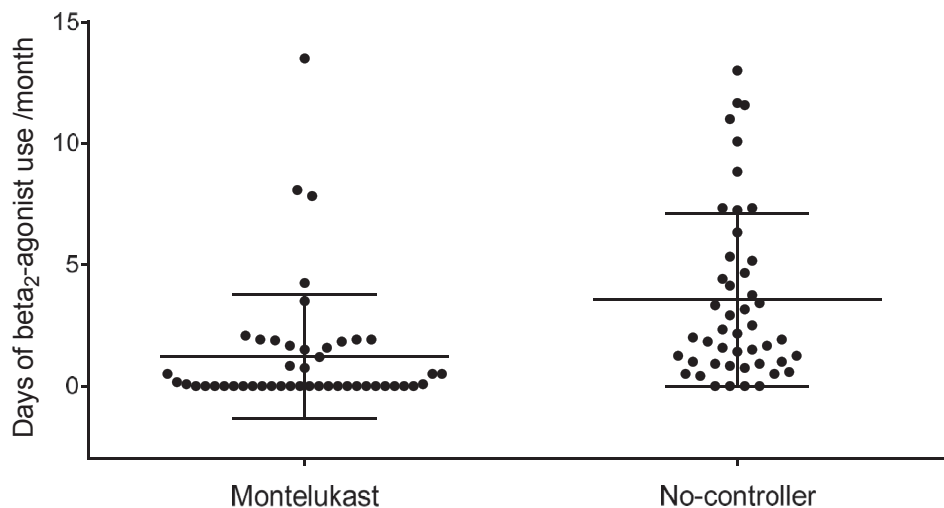


Fig. 5. Days of beta2 agonist use per month. Each dot indicates the days of beta2 agonist use per month in each patient randomized to the montelukast or no-controller group. Horizontal lines in each treatment group indicate the mean $\pm$ 1 standard deviation ($P < 0.0001$, Mann–Whitney U test).

acute sinusitis, mycoplasma pneumonia, and croup. All adverse events were mild or moderate in intensity. No patients discontinued the study because of adverse events. Respiratory infections may have caused asthma exacerbation but there was no statistical difference in the number of respiratory infections between the groups.

Discussion

In this study, control treatment with montelukast effectively reduced acute exacerbations in children aged 1–5 years who had asthma symptoms more than once a month but less than once a

week. Compared with as-needed β_2 -agonists, montelukast reduced the number of acute exacerbations by one in 1 year. This treatment effect is not large. However, it has clinical meaning because acute exacerbations cause a considerable burden on children and their families including urgent care or emergency room visits. In addition, acute exacerbations sometimes increase the risk of life-threatening respiratory failure.¹⁴

Preschool children with symptoms less than once or twice a week are classified into “intermittent asthma” by the GINA report and EPR-3.^{1,2} In this patient population, few clinical trials have evaluated the efficacy of control treatment. In one study, montelukast reduced asthma exacerbations in children with 2–5 years

Table 2
Adverse events.

Treatment	Patient ID	Adverse event	Severity	Causality
Montelukast	02	Upper respiratory infection	Mild	Related
	05	Mycoplasma pneumonia	Moderate	Related
	02	Hand-foot-and-mouth disease	Mild	Not related
	02	Urticaria	Mild	Not related
	09	Acute sinusitis	Mild	Not related
	02	Gastroenteritis	Mild	Not related
No-controller	13	Croup	Mild	Not related
	15	Influenza type A	Mild	Related
	11	Influenza type A	Mild	Not related
	01	Influenza type B	Mild	Not related
	01	Streptococcus hemolyticus infection	Moderate	Not related
	01	Mycoplasma infection	Mild	Not related
	06	Pneumonia	Moderate	Not related
	06	Chicken pox	Mild	Not related
	15	Rotavirus infection	Mild	Not related

of age who had intermittent asthma symptoms resulting from an upper respiratory infection.¹³ In another study, montelukast reduced recurrent wheezing episodes in infants with the first episodes of acute respiratory syncytial virus bronchiolitis.¹⁵ However, these studies have not shown that children need regular treatment because viral-induced exacerbations are seasonal.¹³ On the basis of these findings, we showed the efficacy of regular treatment with montelukast.

In the secondary analysis, the proportion of patients who received step-up treatment was significantly lower and use of beta2 agonists was significantly lower in the montelukast group. Although previous studies have shown that montelukast improved asthma control in patients with asthma symptoms,^{16,17} these studies did not include children younger than 6 years of age. Our result indicated that montelukast prevented disease progression in younger children and that control treatment should be started in earlier disease stage.

These favorable effects of montelukast might be derived from its pleiotropic action. In the previous non-clinical studies, it ameliorated airway remodeling by blocking eosinophils-induced epithelial to mesenchymal transition,¹⁸ decreasing airway smooth muscle mass,¹⁹ and reducing the cytokine levels in bronchus.²⁰ It also suppressed the initial immune response activated by dendritic cell functions and T-helper cell 2 cytokine production activated by type 2 innate lymphoid cells in the lung.^{21,22}

Montelukast was well tolerated. Most adverse events in the montelukast group were communicable diseases such as upper respiratory infection, hand-foot-and-mouth disease, acute sinusitis, or croup. No patients discontinued the study because of adverse events. A previous review using the data of placebo-controlled pediatric studies and their extension studies indicated that the safety profile for montelukast was similar to that for placebo or usual care therapies.²³ This review also showed that adverse events most frequently reported in preschool children included upper respiratory tract infections. Our results were consistent with these findings.

Some limitations should be mentioned. First, we used the open label design, which might induce detection bias. However, the study office adjudicated the number of acute asthma exacerbations on the basis of the records in the booklets. Thus, we consider that this third-party adjudication reduced such bias. Second, the treatment period was not long enough to detect adverse events occurring later in the treatment. Although the safety profile of montelukast has not been reported to change with long-term use,²³ control treatment sometimes continues for years. Therefore, long-

term interventional or observational studies will be warranted. Finally, our study was not designed to identify the predictive factor for responding to montelukast. Results of a recent randomized controlled trial suggested that copy numbers of the Sp1-binding motif in the arachidonate 5-lipoxygenase gene promoter might be useful to identify a montelukast-responsive subgroup in young children.²⁴ Because preschool children with wheeze consume a disproportionately high amount of health-care resources,²⁵ biomarkers or genomic risk profiles should be developed to improve asthma treatment in each patient.²⁶

In conclusion, we found that montelukast is an effective control treatment for preschool children who have asthma symptoms more than once a month but less than once a week. Further study will be needed to identify the subgroup positively responding to montelukast. Interventional or observational studies to evaluate its long-term safety will also be needed.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.alit.2017.04.008>.

Conflict of interest

TF received lecture fees from GlaxoSmithKline, MSD, Maruho, a payment for his writing a manuscript from AstraZeneca, and research funding from Pfizer. The rest of the authors have no conflict of interest.

Authors' contributions

TF conceived and designed the study. MN and TF analyzed the data and wrote the manuscript. MI, NF, CH, TKi and TKa recruited the subjects and collected the data. All authors made substantial contributions to the design, collection and interpretation of data; they all critically reviewed and approved the final manuscript.

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