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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; SpO_2, 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.

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 (SpO_2) 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 SpO_2; 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 SpO_2 <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

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