

A Randomized Open-Label Comparative Study of Montelukast versus Theophylline Added to Inhaled Corticosteroid in Asthmatic Children

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ABSTRACT

Background: Inhaled corticosteroids (ICSs) are widely used in combination with other classes of drugs for treatment of childhood asthma. The efficacy and the safety of montelukast added to low-dose ICS therapy were compared with those of sustained-release theophylline added to low-dose ICS therapy in asthmatic children in the present study.

Methods: Following the 2-week run-in period, 6-to 14-year old patients receiving treatment with ICSs were randomized to treatment for 4 weeks with either montelukast 5 mg once daily or sustained release theophylline 5–8 mg/kg (dry syrup) or 100–200 mg (tablet) twice daily. Patients also received a fixed dose of ICS throughout the run-in and treatment periods. The primary efficacy endpoint was the change from baseline in peak expiratory flow (PEF) at Week 2.

Results: A significant increase in morning PEF was observed in the add-on montelukast group as compared with the add-on theophylline group at Week 2 (change from baseline of 22.8 L/min vs. 8.7 L/min; $p = 0.041$ for between-group difference) and at Week 4 (31.0 L/min vs. 9.8 L/min; $p = 0.012$). A significant increase in evening PEF was observed in the add-on montelukast group as compared with the add-on theophylline group at Week 4 (24.7 L/min vs. 8.7 L/min; $p = 0.027$). There were no significant differences between the treatment groups in incidences of clinical and laboratory adverse experiences.

Conclusions: The results indicate that montelukast added to low-dose ICS is an effective and safe option for the treatment of asthma in children.

KEY WORDS

childhood asthma, inhaled corticosteroid, montelukast, peak expiratory flow, sustained-release theophylline

INTRODUCTION

Bronchial asthma is a chronic inflammatory disease characterized by airway hyper-responsiveness and episodic respiratory symptoms, such as breathlessness, wheezing, chest tightness and coughing.^{1,2} Numerous cell types, including eosinophils, T cells, mast cells, basophils, and neutrophils, play a role in triggering airway inflammation.³ Cysteinyl leukotrienes (CysLTs) and other mediators released by such inflammatory cells have been shown to play a

critical role as determinants of pathological conditions in bronchial asthma.^{4,6} Montelukast is a selective CysLT₁ receptor antagonist that reduces asthmatic inflammation and airway resistance and prevents bronchoconstriction.⁷⁻¹⁰

Inhaled corticosteroids (ICSs) are used as medication for early intervention and long-term management of childhood asthma. ICSs are effective because they directly reach the airway and intensively inhibit airway inflammation.¹¹⁻¹³ However, when the amount of drug deposited in the respiratory tract increases with

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use of higher dose, risks of adverse drug reactions also increase.^{11,14} Therefore, some reports have recommended combination of ICS with other classes of drugs than ICS monotherapy with increased doses.¹⁵⁻¹⁷ Such combined therapy for long-term asthma management has been shown to be more effective in controlling mild to severe persistent asthma in children. Candidates for concomitant drugs include CysLT₁ receptor antagonists, long-acting inhaled β_2 -agonists, and sustained-release theophylline. However, there have been few comparative studies done on these types of drugs when combined with low-dose ICS in children with asthma. In this study, the efficacy and safety of oral administration of montelukast was compared to those of sustained-release theophylline in asthmatic children in the treatment with ICS.

METHODS

PATIENTS

Eighty-four children, male: 51 (60.7%), female: 33 (39.3%), aged 6–14 years, with unstable asthma symptoms despite low dose ICS therapy were enrolled in the study. Patients had mild to severe persistent asthma according to the Japanese Pediatric Guidelines¹¹ and mild to moderate persistent asthma as defined by the GINA guidelines.¹⁸ Before the 2-week run-in period, patients were confirmed to have airway reversibility and reproducible peak expiratory flow (PEF) measurement. During the 2-week run-in period, patients were confirmed to have symptoms (recurrent coughing, or mild or moderate asthma attacks). The following patients were excluded from the study: patients on continuous therapy with oral or injectable corticosteroids; patients who had used oral antiallergic drugs within the 2 weeks prior to the run-in period; patients who used a long-acting corticosteroid within the 1 year prior to the run-in period; and patients with complications that could affect the evaluation of efficacy, such as bronchiectasis. Patients with a history of serious adverse drug reaction to theophylline or other xanthine derivatives and patients who had previously used montelukast were also excluded from the study.

Parents or guardians gave written consent prior to the start of the study. The study was approved by the institutional review board of each participating site.

STUDY DESIGN

This study was done as a multi-center, randomized, open-label study conducted between June 2003 and August 2004. Twenty-four sites around Japan participated, involving a total of 61 affiliated specialists in pediatric asthma treatment. Following a 2-week run-in period, patients were randomized to treatment for 4 weeks with either montelukast 5 mg chewable tablet administered once daily at bedtime or sustained release theophylline 5–8 mg/kg (dry syrup) or 100–200

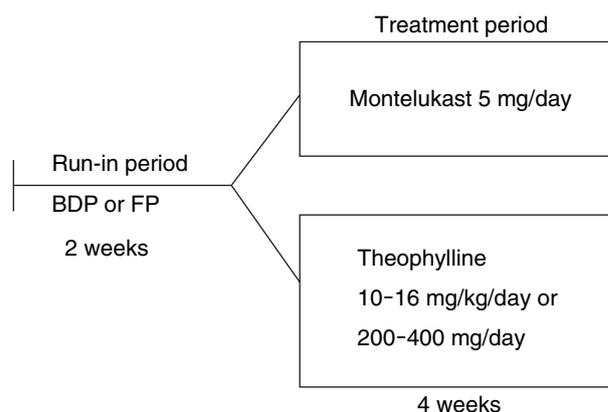


Fig. 1 Study design. BDP = beclomethasone dipropionate; FP = fluticasone propionate.

mg (tablet) twice daily (Fig. 1). Patients also received a fixed dose of inhaled corticosteroid in the run-in and treatment periods (CFC-beclomethasone dipropionate 100–400 $\mu\text{g}/\text{day}$, or fluticasone propionate 100–200 $\mu\text{g}/\text{day}$). The central random allocation of the study drug was performed using the minimization method involving study centers and body weight as factors. Laboratory tests (hematology, blood chemistry, urinalysis) were performed at the beginning and the completion of treatment. Pulmonary function tests (FEV₁ and FVC) were performed at the time of laboratory tests whenever possible.

EVALUATION OF EFFICACY AND SAFETY

The primary efficacy endpoint was the change from baseline in PEF at Week 2. PEF was measured daily with a Mini-Wright PEF meter (Clement Clark International; Harlow, UK) three times upon awakening and three times at bedtime, and the maximum value at each time was recorded. Patients kept a daily asthma diary from the beginning of the run-in period to the completion of treatment, and daily recorded asthma-related symptoms (asthma attacks, coughing, daily activities, nighttime sleep), morning and evening PEF values, treatment compliance with study medication, and use of other concomitant drugs such as inhaled β_2 -agonist.

Clinical and laboratory adverse experiences were recorded during the study. Patients also assessed tolerability at the completion of the 4-week treatment period (or at discontinuation).

STATISTICAL ANALYSIS

The per-protocol set (PPS) was defined as the primary efficacy analysis population. The analyses were also performed in the full analysis set (FAS) to examine the stability of the study results. Summary statistics of the observed values and the changes from baseline (defined as the mean over the 2-week run-in period) as well as their 95% confidence intervals were

Table 1 Patient Demographics and Other Baseline Characteristics (Per-Protocol Set)

Treatment groups	Montelukast	Theophylline
Number of subjects	39 N (%)	36 N (%)
Gender		
Male	21 (53.8)	23 (63.9)
Female	18 (46.2)	13 (36.1)
Age		
6–9 yrs	21 (53.8)	26 (72.2)
10–14 yrs	18 (46.2)	10 (27.8)
Mean ± SD	9.4 ± 2.4	8.8 ± 2.2
Body weight		
< 30 kg	22 (56.4)	22 (61.1)
≥ 30 kg	17 (43.6)	14 (38.9)
Mean ± SD	34.0 ± 14.3	28.7 ± 7.8
Asthma severity		
Mild persistent	24 (61.5)	18 (50.0)
Moderate persistent	12 (30.8)	16 (44.4)
Severe persistent	3 (7.7)	2 (5.6)
Duration of asthma		
Mean ± SD	5.3 ± 3.4	5.6 ± 3.7
Dose of inhaled corticosteroid †		
< 200 µg/day	11 (28.2)	10 (27.8)
≥ 200 to 300 µg/day	13 (33.3)	18 (50.0)
≥ 300 µg/day	15 (38.5)	8 (22.2)
Mean ± SD	261.6 ± 102.3	235.9 ± 86.5
Eosinophils		
< 6%	12 (30.8)	17 (47.2)
≥ 6%	27 (69.2)	19 (52.8)

† Equivalent to dose of beclomethasone dipropionate

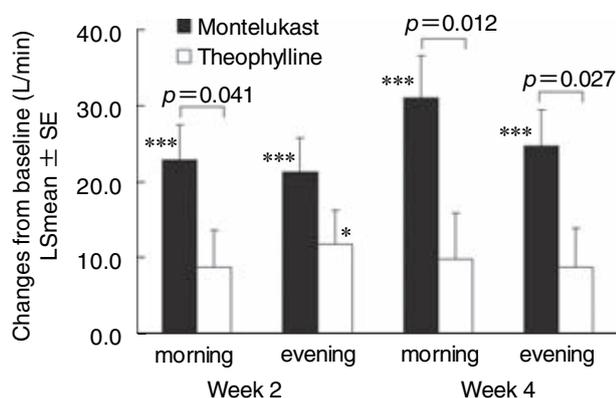


Fig. 2 Comparison of the changes from baseline in morning and evening PEF between montelukast and theophylline. *** $p < 0.001$ and * $p < 0.05$ compared with baseline.

computed at each time point and for each treatment group. Statistical analyses were performed for PEF at Week 2 (defined as the mean over treatment between

Week 1 and 2) and Week 4 (defined as mean over treatment between Week 3 and 4). If there were no data for analysis at Week 4, then the value at Week 2 was extrapolated, using the Last Observation Carried Forward method. Comparisons of the change from baseline between treatment groups were performed using an analysis-of-covariance model involving treatment as a factor and baseline value as a covariate. Within-group comparisons of the values at each time point with baseline were also performed using Student's *t*-test for the least squares mean (hereinafter LSmean) of change.

For those patients included in the analysis of safety, the numbers and percentages of patients reporting adverse experiences were summarized by treatment groups.

RESULTS

Of 84 randomized patients, 79 patients completed the study, while 5 patients withdrew. The reasons for withdrawal were: occurrence of adverse experience in 3 patients, use of prohibited concomitant drug in 1

Table 2 Summary statistics for PEF (morning, evening), numbers of mild asthma attacks and Inhaled β_2 -agonist use

Item	Group	N	Baseline	Week 2	Week 4	Week 4 (LOCF)
Morning PEF (L/min)	M	39	264.7 \pm 12.1	287.4 \pm 11.7	295.6 \pm 12.0	295.6 \pm 12.0
	T	36	261.3 \pm 11.6	270.2 \pm 12.1	273.1 \pm 12.0	269.3 \pm 11.9
Evening PEF (L/min)	M	39	278.2 \pm 12.3	299.2 \pm 11.9	302.5 \pm 12.0	302.5 \pm 12.0
	T	36	270.4 \pm 11.5	282.5 \pm 11.6	278.4 \pm 12.0	279.2 \pm 11.4
Mild Asthma Attacks (times/week)	M	39	0.89 \pm 0.17	0.28 \pm 0.12	0.27 \pm 0.11	0.27 \pm 0.11
	T	36	1.02 \pm 0.25	0.56 \pm 0.32	0.58 \pm 0.24	0.56 \pm 0.22
Inhaled β_2 -Agonist Use (times/week)	M	26	5.93 \pm 1.42	4.37 \pm 1.29	4.15 \pm 1.16	4.15 \pm 1.16
	T	20	5.68 \pm 1.76	4.73 \pm 1.94	3.50 \pm 1.61	4.58 \pm 1.91

M: Montelukast, T: Theophylline, Mean \pm SE

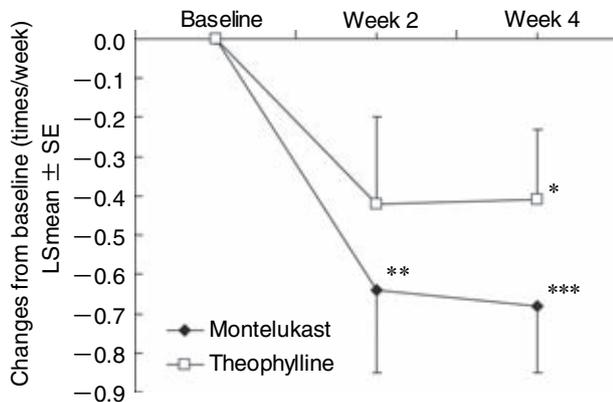


Fig. 3 Comparison of the changes from baseline in mild asthma attacks between montelukast and theophylline. *** $p < 0.001$, ** $p < 0.01$, and * $p < 0.05$ compared with baseline.

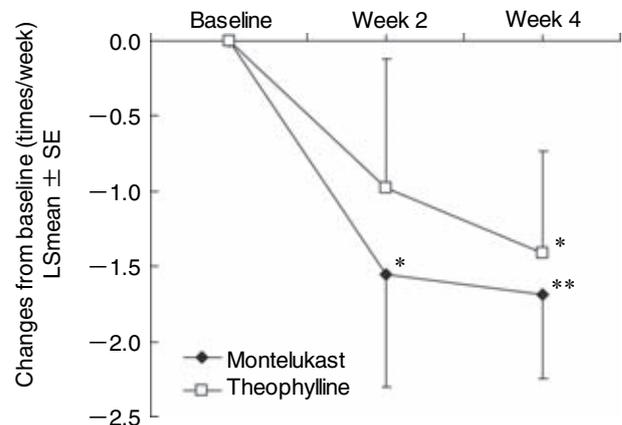


Fig. 4 Comparison of the changes from baseline in inhaled β_2 -agonist use between montelukast and theophylline. ** $p < 0.01$ and * $p < 0.05$ compared with baseline.

patient, and deviation of study visit schedule in 1 patient. Seventy-five patients with data on PEF at Week 2 (primary endpoint) were eligible for efficacy analysis. Nine patients were excluded from the efficacy analysis set, and the reasons for exclusion were: use of prohibited concomitant drug in 3 patients, violation of study procedure in 3 patients, change in living environment in 1 patient, insufficient study period and insufficient frequency of PEF measurements in 1 patient, and noncompliance with drug administration and insufficient frequency of PEF measurements in 1 patient.

Eighty-three patients were eligible for analysis of safety; 1 patient in the theophylline group was excluded because of delayed performance of the patient's laboratory tests.

The dose of inhaled corticosteroid (mean \pm SD, on the beclomethasone dipropionate equivalence basis) in the 75 eligible patients for efficacy analysis was 261.6 \pm 102.3 $\mu\text{g}/\text{day}$ in the montelukast group and 235.9 \pm 86.5 $\mu\text{g}/\text{day}$ in the theophylline group; there was no significant difference between the two groups. There were also no significant differences between

the two treatment groups with respect to other baseline characteristics (including sex, age, body weight, and severity grade of asthma) (Table 1).

PEF IMPROVEMENT

The LSmean change from the baseline in morning PEF at Week 2 was 22.8 L/min in the montelukast group ($p < 0.001$: within group comparison from baseline), and 8.7 L/min in the theophylline group ($p = 0.078$: within group comparison from baseline), demonstrating a significant improvement in the montelukast group compared with the theophylline group ($p = 0.041$: between group comparison). At Week 4, the change from baseline in morning PEF was 31.0 L/min in the montelukast group ($p < 0.001$), and 9.8 L/min in the theophylline group ($p = 0.107$), demonstrating a significant improvement in the montelukast group compared with the theophylline group ($p = 0.012$) (Fig. 2, Table 2).

The LSmean change in evening PEF at Week 2 from baseline was 21.3 L/min in the montelukast group ($p < 0.001$) and 11.7 L/min in the theophylline group ($p = 0.013$). The difference between the groups

in the change from baseline was not significant ($p = 0.137$). At Week 4, the change from baseline in evening PEF was 24.7 L/min in the montelukast group ($p < 0.001$) and 8.7 L/min in the theophylline group ($p = 0.096$), indicating a significant improvement in the montelukast group compared with the theophylline group ($p = 0.027$) (Fig. 2, Table 2).

MILD ASTHMA ATTACKS

A mild asthma attack was defined as an episode of mild wheezing occasionally associated with mild intercostal or tracheosternal retractions. The LSmean change from the baseline in the number of mild asthma attacks (including wheezing) at Week 2 was -0.64 times/week in the montelukast group ($p = 0.004$ for difference from baseline) and -0.42 times/week in the theophylline group ($p = 0.061$ for difference from baseline). The change at Week 4 was -0.68 times/week in the montelukast group ($p < 0.001$) and -0.41 times/week in the theophylline group ($p = 0.024$). No significant differences between the groups were observed in the changes at Week 2 and Week 4 (Fig. 3, Table 2).

INHALED β_2 -AGONIST USE

The LSmean change from baseline in the number of inhaled β_2 -agonist use at Week 2 was -1.55 times/week in the montelukast group ($p = 0.046$) and -0.98 times/week in the theophylline group ($p = 0.261$). The change at Week 4 was -1.69 times/week in the montelukast group ($p = 0.005$) and -1.41 times/week in the theophylline group ($p = 0.044$). No significant differences between the groups were observed in the changes at Week 2 and Week 4 (Fig. 4, Table 2).

PERIPHERAL BLOOD EOSINOPHILS

Eosinophil levels were not significantly affected by either treatment with add-on montelukast or theophylline and no significant difference was observed between the two treatments (data not shown).

SUBGROUP ANALYSIS BY BODY WEIGHT IN THE MONTELUKAST GROUP

Study subjects on montelukast were stratified into subgroups by body weight (<30 kg and ≥ 30 kg), and differences in PEF and in safety were assessed. The changes from baseline values in morning and evening PEF were similar between the subgroups at Week 2 and Week 4; there were also no significant differences between the two subgroups in safety assessments (data not shown).

SAFETY ASSESSMENT

There were no clinically meaningful differences between the treatment groups in the incidence of clinical or laboratory adverse experiences. Two drug-related clinical adverse experiences were seen but they were mild and transient: 1 patient (2.4%) in the

montelukast group developed headache and 1 patient (2.4%) in the theophylline group had queasiness. Two serious clinical adverse events, status asthmaticus and asthma aggravation, were reported in 1 patient in each treatment group; however, these were not judged to be drug-related. Two patients (4.8%) in the montelukast group developed drug-related laboratory adverse experiences: 1 patient had increased total protein (baseline: 6.8 g/dL, Week 4: 8.7 g/dL, normal range value: 6.3–7.9 g/dL); 1 patient had increased total bilirubin (baseline: 0.9 mg/dL, Week 4: 1.7 mg/dL, normal range value: 0.1–1.0 mg/dL) and positive urobilinogen urine (baseline: \pm , Week 4: +, normal range value: \pm). Drug-related serious laboratory adverse experiences were not reported. No drug-related adverse experiences were clinically significant.

DISCUSSION

Theophylline is a widely used medication for the treatment of asthma, mostly because of its ease of use, low cost and good anti-inflammatory effects;¹⁹ thus, it was selected for a positive control, as an add-on agent to ICS in this study. In this study, the mean theophylline dosage was 9.8 mg/kg/day (4.7–15.7 mg/kg/day). Sugimoto *et al.* reported that the mean serum theophylline concentration was 8.8–13.1 $\mu\text{g/ml}$ when 7-to 10-year old asthmatic children were given theophylline at a dose of 16 mg/kg/day in the steady state.²⁰ In addition, Nakashima *et al.* reported that the mean serum theophylline concentration was 5.5–7.3 $\mu\text{g/ml}$ when healthy adult male subjects were administered 400 mg/day (approximately 6.1 mg/kg/day) in the steady state.²¹ The ranges of serum theophylline concentration in the present study were assumed to be between the values of the above two studies.^{20,21} In this study, the investigators determined whether or not to perform serum concentration measurement for patients mainly consisting of those whose asthma symptoms were not improved. As a result, the serum theophylline concentration was measured in three patients: 1.3 and 3.1 $\mu\text{g/ml}$ (this patient was measured twice at a dose of 8.2 mg/kg/day), under the detection limit of 2.0 $\mu\text{g/ml}$ (10.4 mg/kg/day), and 6.5 $\mu\text{g/ml}$ (12.0 mg/kg/day), respectively. When used as complementary therapy in patients not optimally controlled by low-to-high dose ICS, montelukast has shown to improve the control of asthma and reduce exacerbations, and to be a good alternative to increasing a dose of ICS or given an additional long-acting β_2 -agonist.^{22,23}

This study shows that montelukast plus ICS demonstrated significant improvement in morning and evening PEF at week 2 and 4 compared to the baseline results with ICS alone. Theophylline plus ICS demonstrated significant improvement in evening PEF at Week 2, compared to the baseline value. Children administered concomitant montelukast and ICS demonstrated a significantly greater improvement in

morning PEF at Week 2 and morning and evening PEF at Week 4 in comparison with concomitant treatment of theophylline and ICS. The improvement in PEF observed with add-on montelukast in the early stage within 2 weeks of the therapy is consistent with the results of a study in adult patients with bronchial asthma, who reported significant improvement in morning PEF from its baseline after 1–3 days of therapy with add-on montelukast.²²

To investigate the influence of severity and duration of disease, subgroup analyses by severity (mild *vs.* moderate and severe) and duration of disease (<5 years *vs.* ≥ 5 years) were performed. In all the subgroups, montelukast showed significant improvement from baseline at Week 2 in the morning PEF, whereas theophylline did not (data not shown). These findings indicate that the addition of montelukast to the therapy resulted in improvement in PEF as early as Week 2, independent of the severity and duration of disease.

Diurnal variation in PEF is an useful indicator for evaluation of asthma, which is possibly related to airway hyper-responsiveness.²⁴ The exploratory data analysis demonstrated that the mean diurnal variation in PEF decreased in the montelukast group from the baseline value of $9.3 \pm 5.2\%$ to $7.2 \pm 4.2\%$ at Week 2 ($p = 0.005$), to $6.1 \pm 3.6\%$ at Week 4 ($p < 0.001$), however it was unchanged in the theophylline group (baseline: $8.8 \pm 7.3\%$, Week 2: 9.0 ± 9.0 , $p = 0.794$, Week 4: 7.3 ± 5.0 , $p = 0.077$). The result suggested that the addition of montelukast to ICS provided more improvement for diurnal variation in PEF than theophylline.

A reduction in mild asthma attacks and in β_2 -agonist use is indicative of improvement in asthma control. Add-on montelukast further reduced the frequency of mild asthma attacks (compared to baseline values) throughout the study, while add-on theophylline was more effective only at Week 4. Also, inhaled β_2 -agonist use during Week 2 or Week 4 (compared to baseline use) was significantly reduced with add-on montelukast, but not with add-on theophylline. These results suggest that montelukast added to ICS can decrease asthma-related symptoms more than theophylline added to ICS in asthmatic children. Therefore, it is concluded that montelukast is more effective than theophylline as add-on therapy to low dose ICS in improving pulmonary measures and asthma-related symptoms in asthmatic children.

Peripheral blood eosinophil levels serve as an indicator of airway inflammation.²⁵ Montelukast is known to decrease peripheral blood eosinophil levels.²⁶ However, eosinophil levels did not show any significant change from the baseline value in both treatment groups in this study. It is thought that the number of patients might not be sufficient to demonstrate significant change.

Montelukast showed additional improvement in PEF to ICS alone because it is believed to have differ-

ent mechanisms of action from those of ICS in suppressing airway inflammation. It is known that despite treatment with corticosteroids, airway inflammation persists in asthmatic patients.²⁷ While ICSs affect many inflammatory pathways in asthma, they have little impact on CysLTs.²⁸ The results from several large-scale clinical studies provide support for this view of a dual pathway of airway inflammation.^{22,23,29}

Montelukast is indicated with one dose of 5 mg for 6- to 14-year old patients, in whom body weight ranged widely. Therefore, in this study the influence of body weight was investigated. The efficacy and safety results from stratifying patients into subgroups (<30 kg and ≥ 30 kg) confirmed the appropriateness of the use of one dose for pediatric patients in that age range. The recent study, which was a multicenter, randomized, double-blind trial for 6- to 14-year old patients with mild asthma, revealed that the efficacy and safety did not differ greatly regardless of body weight when 5 mg montelukast was administered.³⁰

During four weeks of treatment in children with asthma on ICS therapy, both montelukast and theophylline showed a favorable safety profile. In addition, the MOSAIC study,³¹ which was a 12-month, multicenter, randomized, double-blind trial for 6- to 14-year old patients with mild asthma, showed that montelukast was generally well tolerated for the treatment period (12-months), clinical and laboratory drug-related adverse experience represented 4.4% and 0.5% in the montelukast group, respectively.

In summary, this study suggests that when combined with ICS therapy, montelukast is an effective and safe option for long-term management of childhood asthma. Furthermore, taking into account the mode of administration, dose management and convenience of handling, montelukast may be considered superior to sustained-release theophylline as add-on therapy to ICS in asthmatic children.

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REFERENCES

- Gibson PG, Wlodarczyk JW, Hensley MJ *et al.* Epidemiological association of airway inflammation with asthma symptoms and airway hyperresponsiveness in childhood. *Am. J. Respir. Crit. Care Med.* 1998;**158**:36-41.
- Maddox L, Schwartz DA. The pathophysiology of asthma. *Annu. Rev. Med.* 2002;**53**:477-498.
- Hamid Q, Tulic' MK, Liu MC, Moqbel R. Inflammatory cells in asthma: mechanisms and implications for therapy. *J. Allergy Clin. Immunol.* 2003;**111**:S5-17.
- O'Byrne PM. Leukotrienes, airway hyperresponsiveness, and asthma. *Annals New York Acad. Sci.* 1988;**524**:282-288.
- Coffey M, Peters-Golden M. Extending the understanding of leukotrienes in asthma. *Curr. Opin. Allergy Clin. Immunol.* 2003;**3**:57-63.
- Bisgaard H. Pathophysiology of the cysteinyl leukotrienes and effects of leukotriene receptor antagonists in asthma. *Allergy* 2001;**56**:7-11.
- Mechiche H, Naline E, Candenas L *et al.* Effects of cysteinyl leukotrienes in small human bronchus and antagonist activity of montelukast and its metabolites. *Clin. Exp. Allergy* 2003;**33**:887-894.
- Pizzichini E, Leff JA, Reiss TF *et al.* Montelukast reduces airway eosinophilic inflammation in asthma: a randomized, controlled trial. *Eur. Respir. J.* 1999;**14**:12-18.
- Reiss TF, Sorkness CA, Stricker W *et al.* Effects of montelukast (MK-0476); a potent cysteinyl leukotriene receptor antagonist, on bronchodilation in asthmatic subjects treated with and without inhaled corticosteroids. *Thorax* 1997;**52**:45-48.
- Villaran C, O'Neill SJ, Helbling A *et al.* Montelukast versus salmeterol in patients with asthma and exercise-induced bronchoconstriction. Montelukast / Salmeterol Exercise Study Group. *J. Allergy Clin. Immunol.* 1999;**104**:547-553.
- Furusho K, Nishima S. [*Japanese pediatric guideline for the treatment and management of asthma.*] 2002;1-11, 59-74 (in Japanese).
- Bhalay G, Sandham DA. Recent advances in corticosteroids for the treatment of asthma. *Cur. Opin. Investig. Drugs* 2002;**3**:1149-1156.
- Lipworth BJ. Clinical pharmacology of corticosteroids in bronchial asthma. *Pharmac. Ther.* 1993;**58**:173-209.
- Allen DB, Bielory L, Derendorf H, Dluhy R, Colice GL, Szefer SJ. Inhaled corticosteroids: past lessons and future issues. *J. Allergy Clin. Immunol.* 2003;**112**:S1-S40.
- Helms PJ. Corticosteroid-sparing options in the treatment of childhood asthma. *Drugs* 2000;**59**:15-22.
- Greening AP, Ind PW, Northfield M, Shaw G. Added salmeterol versus higher-dose corticosteroid in asthma patients with symptoms on existing inhaled corticosteroid. *Lancet* 1994;**344**:219-224.
- Ukena D, Harnest U, Sakalauskas R *et al.* Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. *Eur. Respir. J.* 1997;**10**:2754-2760.
- Global Initiative for Asthma. *Global strategy for asthma management and prevention.* Available from: <http://www.ginasthma.org>.
- Somerville LL. Theophylline revisited. *Allergy Asthma Proc.* 2001;**22**:347-351.
- Sugimoto H, Shichijo K, Iikura Y, Akimoto K. Pharmacokinetics of MCI-8019 DS (sustained-release theophylline dry syrup) in childhood bronchial asthma. *Jpn. J. Pediatr.* 1994;**47**:557-566 (in Japanese).
- Nakashima M, Nishijima K, Ihashi Y, Izawa O. Bioavailability of Theo-Dur. *Jpn. Pharmacol. Ther.* 1981;**9**:17-25 (in Japanese).
- Price DB, Hernandez D, Maryar P *et al.* Randomised controlled trial of montelukast plus inhaled budesonide versus double dose inhaled budesonide in adult patients with asthma. *Thorax* 2003;**58**:211-216.
- Bjerner L, Bisgaard H, Bouequet J *et al.* Montelukast and fluticasone compared with salmeterol and fluticasone in protecting against asthma exacerbation in adults: one year, double blind, randomized, comparative trial. *BMJ* 2003;**327**:891-896.
- Morikawa A, Nishima S. *Japanese pediatric guideline for the treatment and management of asthma.* 2005;187-188 (in Japanese).
- Shields MD, Brown V, Stevenson EC *et al.* Serum eosinophilic cationic protein and blood eosinophil counts for the prediction of the presence of airways inflammation in children with wheezing. *Clin. Exp. Allergy* 1999;**29**:1382-1389.
- Knorr B, Matz J, Bernstein JA *et al.* Montelukast for chronic asthma in 6- to 14-Year-Old Children. *JAMA* 1998;**279**:1181-1186.
- Strauch E, Moske O, Thoma S *et al.* A randomized controlled trial on the effect of montelukast on sputum eosinophil cationic protein in children with corticosteroid-dependent asthma. *Pediatr. Res.* 2003;**54**:198-203.
- Dworski R, Fitzgerald GA, Oates JA, Sheller JR. Effect of oral prednisone on airway inflammatory mediators in atopic asthma. *Am. J. Respir. Crit. Care Med.* 1994;**149**:953-959.
- Vaquerizo MJ, Casan P, Castillo J *et al.* Effect of montelukast added to inhaled budesonide on control of mild to moderate asthma. *Thorax* 2003;**58**:204-211.
- Nishima S, Furusho K, Furukawa S, Yoshihara S. Cysteinyl leukotriene receptor 1 antagonist; montelukast, on childhood bronchial asthma in multicenter comparative double-blind clinical study (phase IV) with ketotifen fumarate. *J. Clin. Ther. Med.* 2005;**21**:605-636.
- Garcia MLG, Wahn U, Gilles L, Swern A, Tozzi CA, Polos P. Montelukast, compared with fluticasone, for control of asthma among 6- to 14-year-old patients with mild asthma: the MOSAIC study. *Pediatr.* 2005;**116**:360-369.