The effect of montelukast on bronchial hyperreactivity and lung function in asthmatic children aged 6-13 years

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Summary

Background: **Cysteinyl leukotrienes have been shown to play an important role in the pathogenesis of asthma. The effect of the leukotriene receptor antagonist, montelukast, on bronchial hyperreactivity (BHR) as measured by the methacholine challenge test in school children has not been reported.**

Objective: **To determine the effect of montelukast (Singulair®) on BHR measured by methacholine challenge and lung function tests in Thai asthmatic children aged 6-13 years.**

Materials and methods: **This was a randomized, double-blind, placebo-controlled, crossover study performed in 29 mild to moderate persistent asthmatic children aged 6-13 years. Each child received crossover treatment with 6 weeks of montelukast (5 mg/day) and 6 weeks of placebo separated by a two-week washout period.**

Results: **The improvement of FEV1 and FEV1/FVC after 6 weeks of treatment was significantly higher in montelukast group compared to those of placebo group ($p < 0.05$). After 6 weeks of treatment, mean PC20 (± SEM) in the placebo group (5.7 ± 1.41 mg/ml) was lower than in montelukast group (6.8 ± 1.74 mg/ml) but there was no significant difference ($p = 0.79$).**

Conclusion: **Montelukast significantly improved FEV1 and FEV1/FVC but not BHR in mild to moderate persistent asthmatic children aged 6-13 years after the 6 weeks of treatment.** ***(Asian Pac J Allergy Immunol 2011;29:127-33)***

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Abbreviations:
CLs = Cysteinyl leukotrienes
LRA = Leukotriene receptor antagonist
BHR = Bronchial hyperreactivity

Introduction

Asthma is one of the most common chronic diseases in children. The incidence of asthma has increased all over the world. In Thailand, the incidence of asthma in children is about 13 %.[1] Cysteinyl leukotrienes (CLs) have been shown to be important in the pathogenesis of asthma. They were proven to have effects on nasal and airway epithelium by stimulation of c-fibers and increasing vascular permeability which causes fluid leakage and edema, mucous secretion, contraction and proliferation of airway smooth muscles and decreased mucus transport.[2] They also stimulate eosinophil influx which increases cationic protein release and tachykinin secretion that causes epithelial cell damage.[2]

The clinical efficacy of leukotriene receptor antagonist (LRA) in the treatment of asthma has been widely studied. The previous reports show that LRA improves clinical symptoms and lung function in children with asthma.[3-9] Montelukast, one of the LRAs, provides additional asthma control in patients benefiting from, but incompletely controlled by inhaled corticosteroid.[10] The combination of montelukast and inhaled corticosteroid provides complementary and additive action on peripheral blood eosinophils, a parameter of asthma inflammation.[10] GINA guideline 2002[11] placed LRA as an alternative treatment in mild persistent asthma and an add on therapy in moderate and severe persistent asthma. GINA Guideline 2006[12] and 2008[13], which classified asthma depending on level

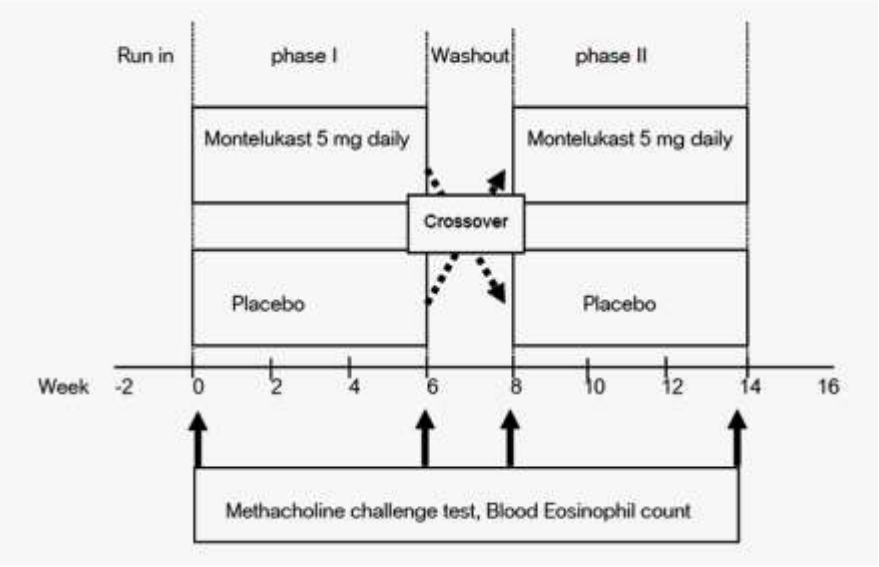

Figure 1. Placebo-controlled, cross over study protocol

of asthma control instead of severity, placed LRA as an alternative treatment in step 2 and add-on therapy in step 3-5 of asthma treatment.

LRAs are considered to be expensive when compared to the cost of living in developing countries. The effect of the LRA, montelukast, on BHR as measured by the methacholine challenge test in school children has not been reported.

The objective of this study was to investigate the effect of the LRA, montelukast (Singulair®), on BHR measured using the methacholine challenge test and lung function measurements in asthmatic children aged 6-13 years.

Methods

A randomized, double-blind, placebo-controlled, crossover study was performed in mild to moderate persistent asthmatic children aged 6-13 years. The patients were diagnosed as having asthma by pediatric allergists. The severity of asthma was characterized following the GINA guidelines 2002[11]. The study was approved by the University Ethics Committee and written informed consent was obtained before the study. The patients were allowed to use inhaled corticosteroids following GINA guideline, short-acting bronchodilator as a symptom reliever and nasal corticosteroids and antihistamines in controlling their allergic symptoms. They had an FEV1 $\geq$ 70% of predicted value prior to the start of the study. The same medications were maintained throughout the study period. Exclusion criteria included patients with severe persistent asthma, poor compliance to their regular medications, inability to perform effective spirometry and usage of long-acting bronchodilators, mast cell stabilizers or theophylline.

After the evaluation of asthma severity, the patients were blinded and randomly divided into 2 groups. There was a two-week observation period on regular medication only, followed by six weeks of daily use of 5 mg montelukast (Singulair®) or placebo (similar shape, color, taste and package to the study drug). Thereafter, there was a two-week observation period followed by six weeks of crossover treatment (montelukast or placebo) as shown in Figure 1. The patients were asked to take 1 tablet of the study medication every night in both six-week study periods. Patients were assigned to record daily clinical symptom scores (0 = no symptoms, 1 = mild, 2 = moderate and 3 = severe), morning and evening peak expiratory flow rates and medication use starting in the initial observation period. The physical examination, pulmonary function tests, clinical symptom scores and medication use monitoring were performed every 2 weeks. Compliance was assessed by counting the number of tablets of the studied medication remaining at each visit. Complete blood count, electrolytes, kidney, liver function test and metacholine challenge test were performed at the end of initial observation period, after the first six-week of treatment, after the second observation period, and at the end of the second six-week

Table 1. Baseline characteristics and lung function tests of the study patients.

Variable	Total patients N = 29	Montelukast before N = 14	Placebo before N = 15
Age, yr ± SD	9.0 ± 1.1	8.9 ± 0.9	9.1 ± 1.1
Height, cm ± SD	133.38 ± 11.97	131.0 ± 13.6	135.6 ± 10.2
Gender			
Male	23	10	13
Female	6	4	2
Severity			
Mild persistent	25	11	14
Moderate persistent	4	3	1
Allergic rhinitis	19	11	8
Familial History of Atopy	20	11	9
Skin prick test			
Dust mite	28	14	14
Cockroach	17	10	7
Seafood	12	5	7
Eosinophil count (Cells/mm^3) ± SEM	634.18 ± 393.77	706.87 ± 465.9	566.34 ± 313.46
Lung function test ± SEM			
FEV1 (L)	1.39 ± 0.30	1.31 ± 0.29	1.42 ± 0.35
FVC (L)	1.59 ± 0.37	1.52 ± 0.35	1.63 ± 0.46
FEV1 /FVC (%)	87.60 ± 7.29	86.00 ± 8.77	87.78 ± 6.12
PEFR (L/min)	191.17 ± 46.85	207.90 ± 62.45	220.67 ± 73.41
FEF 25-75 (% predicted)	89.66 ± 33.2	88.25 ± 27.14	89.17 ± 32.97

treatment period. The last follow up was two weeks after the end of the second treatment period.

Bronchial responsiveness to methacholine was assessed using a previously described protocol.[14] Spirometry was performed using a pulmonary function test system (Minato PAL AS-600 BC). A fall of 20 % in FEV1 from baseline values was considered to be the end of the test.

Statistical analysis

The primary outcomes were the effects of montelukast on the results of metacholine challenge test and pulmonary function parameters. A sample size of 29 patients was calculated as necessary to detect a decrease of 0.5 SD in BHR with a power of 80%. The sequence effect was tested against subjects who were nested within a sequence. This test validated the model in ruling out a significant carry over effect. The results of lung function tests and the number of blood eosinophils were recorded as the arithmetic mean ± SEM. Mean changes were expressed as percentage changes from the baseline. Comparisons within treatments were made by a paired t test and comparison between treatments by ANOVA for crossover design.[15,16] Statistical analyses were performed using SPSS 11.5. Statistical significance was assumed as $p < 0.05$.

Results

Twenty nine asthmatic children (23 boys and 6 girls) aged 6-13 years (mean 9 ± 1.1 years) were enrolled into the study. Twenty five patients had mild persistent asthma and 4 had moderate persistent asthma. Twenty one patients (72 %) had allergic rhinitis and three (10 %) had atopic dermatitis. All of the patients had atopic asthma, 28 had positive skin prick test to house dust mites and 14 to cockroaches. The baseline characteristics and lung function test results for the whole study group, prior to treatment with montelukast or placebo are shown in Table 1. There was no significant difference in baseline lung function test and blood eosinophil count between montelukast and placebo groups. All of the cases used inhaled corticosteroid, as recommended by GINA Guideline 2006.[12]

The mean PC 20 (± SEM) was 6.8 ± 1.74 mg/ml after 6 weeks of montelukast treatment and 5.7 ± 1.41 mg/ml after placebo treatment. PC20 was

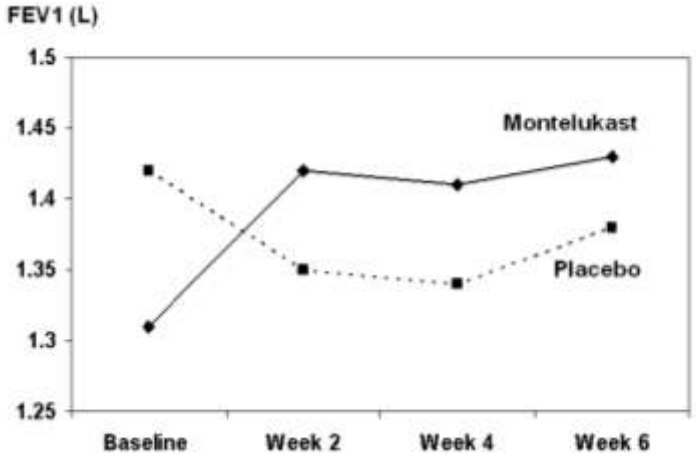

Figure 2. Comparison of FEV1 between montelukast and placebo treatment groups

lower in placebo group but there was no significant difference (p = 0.79). The mean FEV1 and FEV1/FVC at baseline, 2 weeks, 4 weeks and 6 weeks after montelukast and placebo treatment are shown in Figure 2. and 3., respectively. The mean improvement of FEV1, FEV1/FVC at 6 weeks after montelukast was significantly higher than placebo ($p < 0.05$), as shown in Table 2. Improvement was also observed at 2 and 4 weeks but the difference was not statistical significant. Mean improvements from the baseline of PEFR and FVC were higher in the montelukast than in the placebo treatment group but there was no statistical significance. The mean $\pm$ SEM of eosinophil counts before and after 6 weeks of montelukast treatment were 706.87 $\pm$ 465.9 and 567.24$\pm$58.2 cells/mm^2 while the mean $\pm$ SEM of eosinophil counts before and after 6 weeks of placebo were 566.34 $\pm$ 313.46 and 718.89 $\pm$ 131 cells/mm^2 respectively. The mean eosinophil counts decreased after 6 weeks of montelukast treatment but increased after placebo treatment, but this difference was not statistically significant.

Clinical improvement assessed by parents and patients were 86.21% (25/29) in montelukast and 68.79% (20/29) in placebo treatment groups. The clinical asthma symptom scores were not significant different between groups (the average scores before and 4-week after the study were 1.32 VS. 0.53/week in placebo group and 1.71 VS. 0.77/week in the treatment group). The patients in the montelukast group used less β2 agonist as rescue medication than those in the control group (average use of rescue medication was 2 puffs/week before and 0.80 VS. 0.53 puffs/week after treatment in momtelukast and placebo groups respectively). However,this difference was not statistically significant.

In this study, montelukast showed no significant effect on clinical symptoms of allergic rhinitis but significant improvement in 2 out of 3 cases with atopic dermatitis. Montelukast treatment did not have a higher rate of side effects compared to placebo treatment. None of the patients complained of drowsiness or other discomfort. There were no changes in any blood chemistry. Both montelukast and placebo were well tolerated and accepted by the patients, but most of the parents preferred montelukast treatment.

Discussion

This is the first study to investigate the effect of montelukast therapy on bronchial reactivity as determined by PC20 after being challenged by methacholine in school children aged 6 to 13 years with mild to moderate persistent asthma. The study was performed using a randomized, double-blind, placebo-controlled, crossover
design to reduce the difference between patients' characteristics, severity, and seasonal induced symptoms.

In our study, all of the patients had persistent asthma so the patients were allowed to continue inhaled corticosteroids, nasal corticosteroids and antihistamines in controlling their allergic symptoms for ethical reasons. The same medications were maintained throughout the study period to eliminate differences between the two groups.

This study showed that 6 weeks of once-daily treatment with montelukast reduced BHR compared

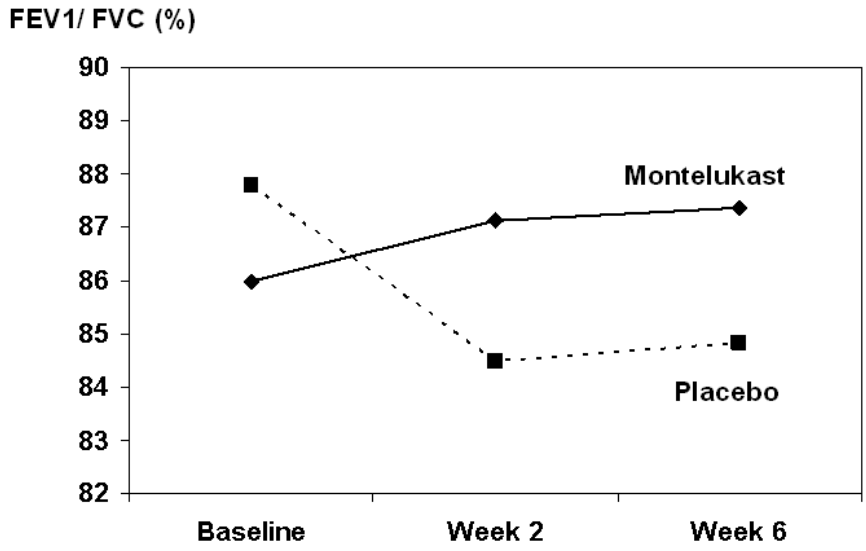

Figure 3. Comparison of FEV1/FVC between montelukast and placebo treatment groups

with placebo treatment, but there was no statistically significant difference between the groups. A previous study in very mild asthmatic children aged 3-6 years who did not receive inhaled corticosteroids showed that 4 weeks of montelukast treatment significantly decreased bronchial hyperreactivity measured by the methacholine challenge test when compared with placebo.[4] Another study also showed a significant effect of montelukast therapy on reduction of BHR challenged by hyperventilation with dry cold air in 13 preschool children.[5] The lack of significant improvement in PC20 in this study could be due to the severity of cases, the heterogeneity of the presentation of childhood asthma and the use of inhaled corticosteroids. Inhaled corticosteroids as controller in the treatment of asthma can decrease BHR so the effect of adding on montelukast might not be statistically significant. The variability of the clinical response to LRAs may also depend on the individual's genetic background because it is related to polymorphisms in the leukotriene pathway candidate genes.[17]

We used methacholine challenge to assess BHR in our study because it was well established for identifying airway hyperresponsiveness which was associated with self-reported respiratory morbidity and clinically defined asthma.[18] Methacholine challenge is also useful in monitoring response to therapy in asthmatic patients.[6] Asthma control was shown to be better when a decrease in BHR is demonstrated.

Our study showed that FEV1 and FEV1/FVC were significantly improved from the baseline in the treatment group when compared with the placebo group. The improvement was evident at 2 and 4 weeks after the treatment. Other lung function parameters such as PEFR and FVC also improved but there was no statistical significance. The improvement in FEV1 was in line with previous studies in school age children 6-14 years of age.[3,7,8] A multi-center, randomized, double-blind study in 336 children aged 6 to 14 years old showed that during 8 weeks of treatment, montelukast (5 mg/day) significantly increased FEV1 compared with placebo ($p < 0.001$) and the improvement began 2 weeks after the treatment started.[3] Another 8-week multi-center, randomized, double-blind, parallel group study in 138 children 6–14 years old with persistent asthma showed that montelukast significantly improved FEV1, increased PEFR, reduced nocturnal awakenings, and improved quality of life in children with >75 % of predicted FEV1.[7]

The study medication had no significant side effects when compared with placebo. The compliance with montelukast was very good because the medication is tasty, chewable and only required a once daily dose. This confirms the results of previous the studies of montelukast in asthmatic children aged 2-18 years[19] and 12-week study in mild persistent asthmatic patients aged 8 to 14 years.[20]

Table 2. Lung function after 6 weeks of montelukast and 6 weeks of placebo treatment.

	Montelukast			Placebo			*P* value
	Baseline ± SEM	Montelukast ± SEM	Mean change (% change)	Baseline ± SEM	Placebo ± SEM	Mean change (% change)	of mean changes
FEV1 (L/ min)	1.31 ± 0.29	1.43 ± 0.35	+ 6.68	1.42 ± 0.35	1.38 ± 0.34	- 2.74	0.042*
FVC (L)	1.52 ± 0.35	1.63 ± 0.48	+ 0.11	1.63 ± 0.46	1.64 ± 0.45	+ 0.0002	0.08
FEV1/ FVC (%)	86.00 ± 8.77	87.36 ± 8.09	+ 2.18	87.78 ± 6.12	84.82 ± 7.05	- 3.18	0.018*
PEFR (L/min)	207.90 ± 62.45	250.68 ± 70.98	+ 25.05	220.67 ± 73.41	240.37 ± 76.01	+ 0.12	0.63
PEF 25-75 (% predicted)	88.25 ± 27.14	92.50 ± 35.89	+ 10.18	89.17 ± 32.97	88.70 ± 20.38	-1.39	0.17

This study showed no statistically significant reduction in blood eosinophil counts in the treatment group as compared with the placebo group. This was not the same as the previous studies which showed reduction of eosinophils in the blood and airways of patients with asthma using montelukast.[21,22] The reduction in eosinophils might be masked by the effect of inhaled corticosteroids. The results for allergic rhinitis in our study might be different from other studies[23,24] because our allergic rhinitis patients were also treated with intranasal corticosteroids. The symptoms of atopic dermatitis in our patients improved after montelukast which supports the results of a previous study[25] but the number of those with atopic dermatitis in our study was too small to make a firm conclusion.

The crossover period in this study was designed to eliminate the difference between the two study groups. The 2-week 'washout' period was appropriate in the crossover study in the montelukast study because its anti-inflammatory effect on asthmatic patients is short-lived. The airway reactivity and exhaled nitric oxide levels return to the baseline after discontinuation of montelukast therapy for 1 and 2 weeks, respectively.[26]

In summary, montelukast significantly improved FEV1 and FEV1/FVC but not BHR as measured by the methacholine challenge test in mild to moderate persistent asthmatic children after 6 weeks of montelukast treatment without significant side effects. This medication is useful as an 'add-on' medication in mild and moderate persistent asthmatic children.

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