ASIAN PACIFIC JOURNAL OF ALLERGY AND IMMUNOLOGY (2009) 27: 173-180

Montelukast as Monotherapy in Children with Mild Persistent Asthma

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SUMMARY The cysteinyl leukotrienes cause bronchoconstriction, increased mucus production and airway inflammation, three major features of asthma. Several randomized controlled trials have shown the efficacy of leukotriene receptor antagonists for improving asthma outcomes. The drug is favored for treating childhood asthma, where poor compliance with inhalation therapy is a therapeutic challenge. To assess the effectiveness of Montelukast in asthmatic children under real-life conditions, a prospective, single-arm, multicenter, open-label observational study was performed on asthmatic children 2 to 14 years old with a history of physician-diagnosed mild persistent asthma. Montelukast was given once daily for 12 consecutive weeks. By the end a significant improvement of the daytime asthma symptom score, nighttime asthma score, peak expiratory flow rate (PEFR) and mean score of the investigators' global evaluation was noted ($p < 0.05$). These results suggest that montelukast is an effective monotherapy controller in children with mild persistent asthma.

Asthma is one of the most common chronic diseases. It is estimated that 300 million people are affected by this disease worldwide,[1] and the prevalence is increasing, especially among children. Asthma presents a considerable burden on a child, the child's family, and society. Asthma is a chronic inflammatory disease of the airways; [2-4] pathologic inflammatory changes of the lungs are observed even in patients with mild asthma. Despite considerable advances in the development of new therapeutics as well as in the understanding of the pathophysiology of asthma, asthma remains a serious public health problem, especially in developed countries. The National Asthma Education and Prevention Program (NAEPP) and the Global Initiative for Asthma (GINA) guidelines recommend a controller (anti-inflammatory) treatment for persistent asthma.[2,3] A worldwide survey reported that the use of anti-inflammatory preventives for such children and adults did not achieve its desired objectives.[5] Since some of the current therapies for asthma require inhalation, serum drug level monitoring, and multiple daily administration, these therapies have practical limitations.

The cysteinyl leukotrienes are important mediators of asthma. Their role in the pathogenesis of asthma has been extensively reviewed in the literature.[6-10] They have been shown to cause bronchoconstriction, increased mucus production, and airway in-

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flammation, three major features of asthma. Several randomized controlled trials (RCTs) have demonstrated the efficacy of leukotriene receptor antagonists (LTRAs) as monotherapy[11-15] or added to inhaled corticosteroids (ICSs)[16-18] for improving asthma parameters, including lung function, symptoms, asthma exacerbations, and health-related quality of life. While these trials were performed under strict and vigorous conditions, their implications for effectiveness, as opposed to efficacy, in real-life situations may be limited.[19] Montelukast is an orally administered, specific leukotriene receptor antagonist and was the focus of the current study. The purposes of this study were to (1) evaluate the effectiveness of montelukast in the treatment of asthmatic children in a community setting that could augment the findings of RCTs, and (2) collect information about the productivity loss of caregivers due to asthma episodes of dependents.

PATIENTS AND METHODS

Study design

This study was a prospective, single-arm, open-label observational multicenter study. Data were collected on clinical effectiveness and caregiver productivity loss for asthmatic pediatric patients receiving montelukast. The study was approved by the Joint Institutional Review Board in Taiwan. Written informed consent was obtained from each participant's parents.

Patients

Children aged 2 to 14 years with physician-diagnosed asthma (at least 3 episodes of asthma symptoms during the previous year, including, but not limited to cough, chest tightness, wheezing, and shortness of breath) with mild persistent severity (asthma symptoms more than once a week but less than once a day or nocturnal symptoms more than twice a month but less than once a week) were recruited. All patients were in good health other than asthma, on the basis of their medical history and physical examination. Patients with chronic lung diseases (changes in the lungs that have occurred due to long term mechanical ventilation of the premature or ill infant eg: bronchopulmonary dysplasia), unsolved sinus disease (*e.g.* chronic sinusitis), moderate to severe persistent asthma (asthma symptoms daily or nocturnal symptoms more than once a week), requiring additional asthma therapy other than montelukast or a short-acting beta agonist, an allergic history to LTRAs or an inability of the caregiver to complete the questionnaires and follow the instructions for medication compliance of the patient were excluded.

Treatment and measurements

After enrollment, montelukast sodium 4-mg (Singulair®, Merck Sharp & Dohme) tablets were administered to patients 2 to 5 years old once daily, and 5-mg tablets were administered to patients 6 to 14 years old once daily for 12 consecutive weeks. Physicians subjectively classified the degree of asthma, as well as objectively assessed the severity of asthma based on the patients' reported symptoms. Each patient was given a questionnaire booklet which included the patient's basic data, duration of asthma, allergic nasal problems, medications and the following measurements: (1) asthma symptom score, (2) clinic-measured morning PEFR, (3) mean score of the investigators' global evaluation, (4) short-acting beta agonist (SABA) usage, (5) medical resource utilization for asthma, (6) days lost from school, and (7) caregiver's days lost from work. Patients were assessed at baseline and at 4, 8, and 12 weeks after the start of montelukast treatment.

The asthma symptom scores included (1) Daytime symptom score, consisting of a four-question symptom score worth a total of 6 points on a 0-5 scale for each question. Information on the seriousness of the asthma symptoms of the past 7 days, such as cough, wheezing, breathlessness, and the impact on the patient's daily activity were collected and given the following scores: For cough, wheezing, breathlessness: 0 (no symptoms) to 5 (very severe symptoms); for impact on patient's daily activity: 0 (no impact) to 5 (very serious impact). (2) Nocturnal asthma symptom score, which indicated the severity/frequency of the child's coughing during sleep for the past 7 days was also calculated and evaluated as 0 (no coughing) to 4 (coughing almost the whole night). The average number of puffs of as-needed SABA usage for the past 7 days, as well as hospitalizations and emergency room visits during the 4 weeks before the clinic visit were also reported at each follow-up.

Caregivers who were employed or self-employed were asked to report the school days lost, daily activity lost by the children, and the work days lost in hours (or days) due to childcare at enrollment, at week 4, and at week 12. All measurements were recorded by the caregivers except global evaluation of disease status, which was conducted by the investigators using a scoring table. Improvement in asthma was rated by the investigator at every follow-up visit with a 7-point scale assessment based on clinical examination and patients' symptoms: −3 = greatly worsened, −2 = moderately worsened; −1 = slightly worsened, 0 = no change, +1 = slightly improved, +2 = moderately improved, +3 = greatly improved. Clinical adverse events and any intolerance were collected by a research assistant at each follow-up.

Data analysis

Patients with at least one post-treatment measurement were included in the analysis and stratified by study drug dosage. The mean change from the baseline of the symptom scores, PEFR, impact on work, and productivity loss were assessed. Wilcoxon signed rank test with Bonferroni correction was employed in the four pairwise comparisons of baseline, week 4, week 8 and week 12, where the statistical significance was set as $P < 0.0083$. All data were presented as mean ± S.D. Statistical analysis was performed using the statistical software package SAS version 8e (SAS Institute Inc. Cary, NC).

RESULTS

From a total of 21 hospitals throughout Taiwan, 1143 patients entered this study. Of these, 71 patients were excluded due to protocol violation, and 114 patients were lost to follow up, such that the final analysis included a total of 958 asthmatic children (Fig. 1). The mean age of the cohort was 5.8 ± 2.7 years. From the questionnaire, children were regarded as a victim of allergic rhinitis when children/parents answered "yes" to the question "Have you/has your child ever had a problem with sneezing or a runny, or blocked nose when you/your child did not have a cold or flu?" Concomitant allergic rhinitis was noted in 80.0% of the patients. Baseline characteristics of the patients are listed in Table 1. Of the 597 children aged 2-5 years and 361 children aged 6-14 years, only 86 (14.4%) and 216 (59.8%) respectively, were able to perform the PEFR at baseline. The results of twelve weeks of treatment with montelukast were compared with the scores at baseline. The daytime asthma symptom score (5.5 ± 3.7 *vs.* 1.1 ± 1.8), nighttime asthma symptom score (1.9 ± 1.1 *vs.* 0.5 ± 0.7), PEFR (182 ± 75 *vs*. 208 ± 75), and mean score of the investigators' global evaluation (1.4 ± 0.9 *vs.* 1.9 ± 0.9) (Table 2) improved all significantly during the 12-week treatment period. Compared with the baseline, SABA usage (0.9 ± 3.0 *vs*. 0.4 ± 2.1) and medical resource utilization for

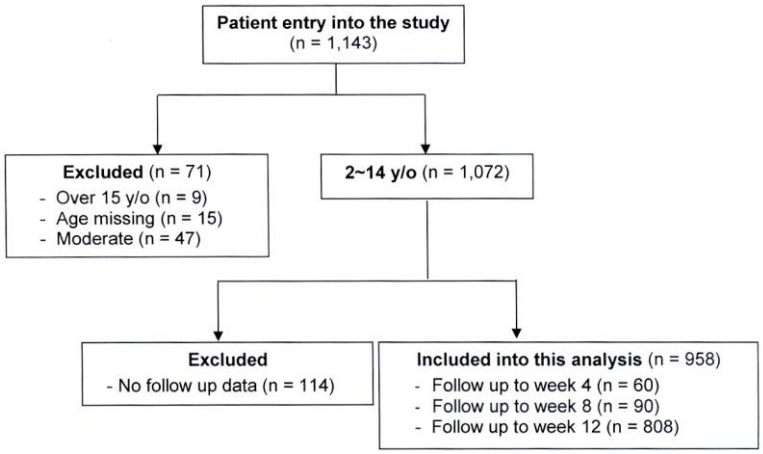

Fig. 1 Subject disposition. The study enrolled a total of 1,143 patients; 185 of these were excluded for various reasons as shown in the figure, resulting in a final analysis of data from 958 patients.

Table 1 Patient characteristics

	Montelukast 4 mg (age 2-5 years) (n = 597)	**Montelukast 5 mg** (age 6-14 years) (n = 361)	**All** (n = 958)
Age (mean ± SD, years)	4.1 ± 1.2	8.7 ± 2.0	5.8 ± 2.7
Gender (%)			
Female	234 (36.2%)	146 (40.4%)	380 (39.7%)
Male	363 (60.8%)	215 (59.6%)	578 (60.3%)
Duration of asthma (mean ± SD) (years)	1.2±1.0	2.6±2.3	1.7±1.7
Concommitant allergic rhinitis	418/534 (78.3%)	270/327 (84.4%)	688/861 (80.0%)

Table 2 Asthma symptom scores and peak expiratory flow rates at different visits

	Montelukast 4 mg (age 2-5 years) (n = 597)	**Montelukast 5 mg** (age 6-14 years) (n = 361)	**All** (n = 958)
Daytime asthma symptoms (n)			
Unit: point			
Baseline	5.5 ± 3.7 (587)	5.4 ± 3.7 (359)	5.5 ± 3.7 (946)
Week 4	2.5 ± 2.4** (591)	2.6 ± 2.5** (356)	2.5 ± 2.4** (947)
Week 8	1.6 ± 2.2** (524)	1.7 ± 2.3** (325)	1.6 ± 2.2** (849)
Week 12	1.0 ± 1.7** (468)	1.1 ± 2.0** (296)	1.1 ± 1.8** (764)
Night time asthma symptoms†(n)			
Unit: point			
Baseline	2.0 ± 1.1 (590)	1.8 ± 1.2 (357)	1.9 ± 1.1 (947)
Week 4	1.0 ± 0.9** (590)	0.9 ± 0.9** (356)	1.0 ± 0.9** (946)
Week 8	0.8 ± 0.9** (525)	0.7 ± 0.8** (326)	0.7 ± 0.8** (851)
Week 12	0.5 ± 0.7** (471)	0.5 ± 0.7** (297)	0.5 ± 0.7** (768)
Peak Expiratory Flow Rate (n)			
Unit: liters/minute			
Baseline	123 ± 40 (86)	205 ± 73 (216)	182 ± 75 (302)
Week 4	135 ± 39** (92)	222 ± 69** (216)	196 ± 73** (308)
Week 8	144 ± 46** (89)	232 ± 72** (195)	204 ± 76** (284)
Week 12	148 ± 44** (81)	235 ± 71** (173)	208 ± 75** (254)
Mean Score of Investigators' Global Evaluation After Montelukast Treatment			
Unit: point			
Week 4 (n)	1.4 ± 0.9 (518)	1.4 ± 0.9 (302)	1.4 ± 0.9 (820)
Week 8 (n)	1.7 ± 0.9* (485)	1.6 ± 0.9* (288)	1.6 ± 0.9* (773)
Week 12 (n)	1.9 ± 0.9* (435)	1.8 ± 0.9* (261)	1.9 ± 0.9* (696)

**P < 0.0083 by Wilcoxon signed rank test with Bonferroni correction to assess the mean change from the baseline.
* P < 0.0083 by Wilcoxon signed rank test with Bonferroni correction to assess the mean change from week 4.
# Daytime asthma symptoms: symptom score based on a 6-point scale (0~5) from four questions. (For questions 1, 2, and 3: 0 = no symptom, 5 = very severe; for question 4, 0 = no impact, 5 = very serious impact. The four questions were: (1) How serious did your child experience asthma symptoms (or cough)? (2) How serious did your child experience wheezing? (3) How serious did your child experience breathlessness? (4) How did your child's asthma affect his/her daily activities?
†Nighttime Asthma Symptom Score: Caregivers were asked to score the severity/frequency of the child's coughing during sleep for the past 7 days: 0 = no cough, 4 = cough almost whole night.
Improvement in asthma was rated by the investigator at every follow-up visit with a 7-point scale assessment based on clinical examination and patients' symptoms: −3 = greatly worsened, −2 = moderately worsened; −1 = slightly worsened, 0 = no change, +1 = slightly improved, +2 = moderately improved, +3 = greatly improved.

asthma (hospitalization 0.10 ± 0.32 *vs*. 0.02 ± 1.2; emergency room visits 0.08 ± 0.28 *vs*. 0.01 ± 0.12)

decreased significantly by week 12 (Table 3). A decrease in the children's school days lost and the caregivers' days lost from work after treatment was also observed (Table 4). During the entire study period, no intolerability or adverse event was reported from any of the study patients.

DISCUSSION

International guidelines recommend the use of inhaled corticosteroids as the preferred controller therapy in mild persistent asthma. However, a therapeutic challenge has arisen with this therapeutic choice as poor compliance with inhalation therapy, as well as potential adverse systemic side effects of high doses of inhaled corticosteroids have been identified in asthmatic children. RCT is considered the gold standard methodology for determining the efficacy and tolerability of new treatments. However, RCT cannot provide information on the effectiveness of interventions in real life.

This study demonstrates the real-life effectiveness of montelukast used as monotherapy in 2- to 14-year-old patients with asthma in a community setting. The daytime and nighttime asthma symptom scores significantly improved at every clinic visit after the patients received montelukast as a 4- or 5-mg chewable tablet, once daily at bedtime. The magnitude of changes observed appeared obvious even as early as 4 weeks after the start of treatment. Although the PEFR was only measured in some of our patients (due to young age, 14.4% in the 2- to 5-year-old group, 59.8% in the 6- to 14-year-old group), the increase reached statistical significance in both age groups. Significant differences in SABA usage for the 7 days before clinic visits and medical resource utilization for asthma were also observed during the study period. No adverse events were reported in this study, which may be due to underreporting in this post-marketing study as all clinical safety information needed to be captured indirectly through parents or guardians instead of directly through the study subjects.

Table 3 SABA usage and medical resource utilization for asthma

	Montelukast 4 mg (age 2-5 years) (n = 597)	**Montelukast 5 mg** (age 6-14 years) (n = 361)	**All** (n = 958)
SABA usage:average number of puffs (n)			
Unit: puff; 500μg/puff			
Baseline	0.5 ± 2.1 (406)	1.5 ± 3.8 (285)	0.9 ± 3.0 (691)
Week 4	0.2 ± 1.5[a] (405)	1.1 ± 3.2[a] (279)	0.6 ± 2.4[a] (684)
Week 8	0.3 ± 1.9 [a] (350)	0.9 ± 3.0[a] (252)	0.6 ± 2.4[a] (602)
Week 12	0.3 ± 1.6 (300)	0.7 ± 2.6[a] (228)	0.4 ± 2.1[a] (528)
Hospitalization (n)			
Unit: time			
Baseline	0.11 ± 0.32 (593)	0.09 ± 0.32 (361)	0.10 ± 0.32 (954)
Week 4	0.01 ± 0.10[a] (593)	0.01 ± 0.12 [a] (356)	0.01 ± 0.11 [a] (949)
Week 8	0.01 ± 0.09[a] (529)	0.01 ± 0.11 [a] (326)	0.01 ± 0.10 [a] (855)
Week 12	0.02 ± 0.14[a] (476)	0.01 ± 0.08 [a] (297)	0.02 ± 0.12 [a] (733)
ER visit (n)			
Unit: time			
Baseline	0.08 ± 0.27 (593)	0.09 ± 0.29 (361)	0.08 ± 0.28(954)
Week 4	0.02 ± 0.12[a] (593)	0.03 ± 0.16[a] (356)	0.02 ± 0.14[a] (949)
Week 8	0.01 ± 0.11[a] (529)	0.01 ± 0.11[a] (326)	0.01 ± 0.11[a] (855)
Week 12	0.01 ± 0.14[a] (476)	0.01 ± 0.10[a] (297)	0.01 ± 0.12[a] (773)

[a] $P < 0.0083$ by Wilcoxon signed rank test with Bonferroni correction to assess the mean change from the baseline.

Table 4 School days lost by children and work days lost by caregivers at different visits

	Montelukast 4 mg (age 2-5 years) (n = 597)	**Montelukast 5 mg** (age 6-14 years) (n = 361)	**All** (n = 958)
School days lost by children who had to go to school (n)			
Unit: day			
Baseline	1.0 ± 1.5 (401)	0.7 ± 1.4 (335)	0.8 ± 1.5 (736)
Week 8~12	0.2 ± 0.6 (312)	0.1 ± 0.6 (279)	0.2 ± 0.6 (591)
Changes	−0.8 ± 0.1[a] (311)	−0.5 ± 0.1[a] (278)	−0.7 ± 0.1[a] (589)
Daily activity lost by children[b] (n)			
Unit: time			
Baseline	1.7 ± 1.2 (64)	1.7 ± 1.6 (52)	1.7 ± 1.4 (116)
Week 8~12	0.8 ± 0.8 (12)	1.4 ± 0.8 (4)	1.0 ± 0.8 (16)
Changes	−0.4 ± 0.3 (8)	−0.4 ± 0.2 (4)	−0.4 ± 0.2 (12)
Work days lost by caregivers who were employed or self-employed (n)			
Unit: day			
Baseline	0.9 ± 1.7 (299)	0.7 ± 2.4 (200)	0.8 ± 2.0 (499)
Week 8~12	0.2 ± 0.5 (225)	0.1 ± 0.4 (159)	0.1 ± 0.5 (384)
Changes	−0.5 ± 0.1[a] (224)	−0.6 ± 0.2[a] (158)	−0.5 ± 0.0[a] (382)
Planned activities lost by caregivers[c]			
Unit: time			
Baseline	0.5 ± 1.0 (580)	0.4 ± 0.9 (360)	0.4 ± 1.0 (940)
Week 8~12	0.1 ± 0.4 (431)	0.1 ± 0.4 (298)	0.1 ± 0.4 (729)
Changes	−0.3 ± 0.0[a] (430)	−0.3 ± 0.0[a] (297)	−0.3 ± 0.0[a] (727)

[a] $P < 0.0083$ by Wilcoxon signed rank test with Bonferroni correction to assess the mean change from the baseline.
[b] Daily activity refers to: running, jumping, exercise, riding bicycle, outing, mountain climbing, meal gathering, etc, or extra school curricula. The figures represent the number of all types of these activities lost during the defined study period.
[c] represents the number of planned daily activities lost during the defined study period, if any.

A milestone study of children by Knorr *et al.*[20] revealed that the onset of action of montelukast was rapid, and treatment effects occurred within 1 day after the first dose as assessed by two diary card parameters: (1) Total daily as-needed SABA usage, and (2) patient-reported morning PEFR. Compared with montelukast, other controller agents, including inhaled corticosteroid and cromolyn, appear to require a longer treatment duration before their effects become evident.[21-23]

In this study, the treatment effects were maintained consistently over the entire study period. From this study as well as a prior pediatric and adult study no evidence for tachyphylaxis has been reported, suggesting that montelukast maintains its effectiveness in the long-term.[24]

Treatment with montelukast resulted in a statistically significant change in the investigators' global evaluation of the therapy response. We cannot exclude the possibility of potential bias by having the investigators administer the global evaluation questionnaire at each clinic visit, since the investigators were not blinded to the treatment.

Eighty percent of the asthmatic children in this study suffered from concomitant allergic rhinitis. On the basis of epidemiologic, immunologic, and clinical observation, the links between asthma and allergic rhinitis are well documented.[25] Treatment of allergic rhinitis has a direct impact on the control of

asthma. Montelukast could also provide significant improvements of the symptoms and quality-of-life parameters of seasonal allergic rhinitis.[26]

The most current PRACTALL consensus report[27] focusing exclusively on pediatric asthma recommended that LTRAs may be chosen as an alternative first-line treatment for persistent asthma. Evidence also supports the use of oral montelukast as an initial controller therapy for mild asthma in children,[28] as it provides bronchoprotection,[29] and reduces airway inflammation as measured by nitric oxide in some preschool children with allergic asthma.[30,31] Meanwhile, LTRAs offer a therapy for patients who cannot or will not use ICS. The limitations of this study include the lack of blinding of the patients and investigators to the measurements. In addition, the results of the study cannot be extrapolated to patients who met the exclusion criteria of the study, such as requiring other concomitant anti-asthmatic medications. Despite these limitations, this study was a large-scale trial collecting outcomes in routine clinical practice that contribute to the knowledge with regard to the effectiveness of existing therapies in a real-life, community setting.

ACKNOWLEDGEMENTS

We thank the participation of the following investigators: Chien-Cherng Lai, Taipei Medical University Hospital; Shu-Juan Wu, St. Mary's Hospital Lotung; Chung-Chih Kao, Tungs' Taichung Metro Harbor Hospital, Sha Lu Branch; Shirley Tiu, Cardinal Tien Hospital Hsin Chu Mercy Branch; Jen-Sheng Pei, TaoYuan General Hospital, Department of Health; Shao-Fu Lo, En Chu Kong Hospital; Wen-Chiu Wu, Taipei Hospital, Department of Health; Te-Kung Sun, St. Joseph Hospital; Jia-Yuh Jean, Taichung Hospital, Department of Health; Kuo-Yao Wu, Sin Lau Hospital, The Presbyterian Church of Taiwan; Kiew-Ing Ling, Yuan's General Hospital; Ying-Fong Lin, Fooyin University Hospital; Yuan-Chang Lo, Taipei City Hospital, Zhongxing Branch; and Li-Chieh Wang, National Taiwan University Hospital. We also thank Miss Wei-Yu Lei for her assistance with the statistical analysis. This research was funded by Merck Sharp & Dohme Taiwan.

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