Protection of leukotriene receptor antagonist against aspirin-induced bronchospasm in asthmatics

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Purpose: Leukotriene receptor antagonists (LTRAs) are used to treat aspirin-intolerant asthma (AIA); however, the protective effects of long-term LTRA administration against aspirin-induced bronchospasm have not been evaluated. **Objectives:** We investigated the efficacy of a 12-week treatment with a LTRA in protecting against aspirin-induced asthma in AIA patients. **Methods:** Fifty-two adult patients with AIA underwent an aspirin challenge test just before administration of montelukast (10 mg/day) and just after 12 weeks of treatment. The protective effect was assessed as the disappearance of aspirin-induced bronchospasm after 12 weeks of treatment. The results were compared according to the patients' clinical and physiological parameters. **Results:** The decline in FEV1 following aspirin challenge was significantly reduced from 28.6±1.9% to 10.2±1.7% (*P*=0.0001) after 12 weeks of montelukast treatment. However, 14 subjects (30%) still showed a positive response (>15% decline in FEV1) to aspirin challenge. Grouping the subjects into good and poor responders according to post-treatment responses revealed that the pretreatment aspirin-induced FEV1 decline was significantly greater in the poor responders and that the triggering dose of aspirin and the induction time for a positive response were lower and shorter, respectively, in the poor responders. Histories of aspirin hypersensitivity and sinusitis were more prevalent among the poor responders than among the good responders. **Conclusions:** Twelve weeks of treatment with montelukast protected against aspirin-induced bronchospasm in 70% of the AIA cases. A poor response was associated with more severe aspirin-induced bronchospasms before treatment and a history of aspirin hypersensitivity or sinusitis. **Clinical implications:** A severe response to aspirin challenge may be a predictor of poor responsiveness to leukotriene antagonist treatment.

Key Words: Asthma; leukotriene antagonists; aspirin; eosinophils

INTRODUCTION

Aspirin-induced asthma (AIA) refers to the development of bronchoconstriction in asthmatic individuals following the ingestion of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs).[1] Although AIA affects only 5-10% of adults with asthma,[2] aspirin hypersensitivity has attracted a great deal of attention because of its association with increased asthma severity and possible remodeling of both the upper and lower airways.[3] A two-compartment model has been proposed.[4] The overproduction of cysteinyl leukotrienes (CysLTs) has been demonstrated in the airways and circulation of asthmatic patients intolerant to aspirin.[5,6] In addition, compared with aspirin-tolerant asthma (ATA) patients, AIA patients had greater airway hyperresponsiveness on inhalation challenge with CysLTs.[7] These data suggest the presence of augmented target-organ responsiveness to CysLTs. CysLTs exert their biological actions by binding to two types of G protein-coupled receptors, i.e., cysteinyl leukotriene receptor 1 (CYSLTR1), which is sensitive to the asthma drugs montelukast (MLK), zafirlukast, and pranlukast,[8,9] and CYSLTR2.[10]

Clinical trials in adults and children with asthma have established the efficacy of MLK,[11,12] although significant inter-patient

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variability in the response to MLK has been observed in both children and adults with asthma.[13,14] In a group of relatively severe AIA patients, MLK administered as an add-on therapy markedly reduced asthma symptoms and improved lung function.[15] Variable results have been reported regarding the protective effects of leukotriene receptor blockers against aspirin-induced bronchoconstriction.[16-19] However, these studies used small study populations of fewer than 10-15 subjects and short periods of drug administration (about 1 week). Recently, a relatively long-term trial used nasal provocation tests with lysine-aspirin to evaluate the protective effects of 10 mg of MLK daily for 4 weeks in 36 nonsmokers with AIA; this regimen substantially improved nasal function and nasal responses to aspirin in the AIA patients,[20] albeit with wide variation among the patients. To our knowledge, no previous studies have investigated the protection by MLK against aspirin-induced bronchospasm in a relatively long-term trial (12 weeks) using an oral provocation test. Therefore, we examined the protective effect of treatment for 12 weeks with the recommended dose of a CYSLTR antagonist (MLK 10 mg/day) against aspirin-induced bronchospasm in AIA patients; and identified the clinical or physiological factors that determined the outcome of CYSLTR antagonist treatment in these patients.

MATERIALS AND METHODS

Study design

The study subjects were recruited from among asthmatic patients who had been followed regularly at the outpatient clinics of Soonchunhyang University Bucheon and Seoul Hospital, Korea and who had stable mild to moderate asthma according to the GINA guidelines.[21] A clinical history, including age at onset, duration of asthma, history of smoking, and history of aspirin hypersensitivity, was obtained for each subject before entry into the study. Chest posterior-anterior radiography, skin prick testing for allergens, counting of blood eosinophils, determination of the IgE level, and testing for bronchodilator response after inhalation of two puffs of aerosolized albuterol (100 μg) and airway hyperresponsiveness (PC20 methacholine) were conducted within 4 weeks before study. Skin prick tests were performed with 24 common aeroallergens (Bencard Co. Ltd., Brentford, UK), and atopy was defined as one or more positive reactions (>3 mm in diameter). Total IgE was measured using a UniCAP system (Pharmacia Diagnostics, Uppsala, Sweden). The body mass index (BMI) and the presence of sinusitis and nasal polyps were determined.

The oral aspirin provocation test was performed with increasing doses (10 to 650 mg) of aspirin (Astrix; Mayne Pharma Ltd., Melbourne, Australia), using a slightly modified version of the method described previously.[22,23] Changes in FEV1 were monitored for 5 hours after the last dose of aspirin challenge or until the subject complained of intolerable dyspnea. The rate of FEV1 decline following aspirin challenge was calculated as the pre-challenge FEV1 minus the lowest post-challenge FEV1 divided by the pre-challenge FEV1×100. Subjects with a greater than 20% decline in FEV1 without extrabronchial symptoms, or with a greater than 15% decline with extrabronchial nasal or skin manifestations, were defined as showing a positive response[22,23] and were enrolled in the study. After informed written consent was obtained, MLK (10 mg) was administered daily to the subjects for 12 weeks, and then the second aspirin challenge test was performed. During the study period, patients were asked to continue taking any inhaled steroids at the preciously prescribed dosage and to use short-acting bronchodilators as needed. The response to MLK was defined as good or poor when the aspirin-induced rate of FEV1 decline in the second aspirin challenge was <15% or >15%, respectively.

Subjects

A total of 53 subjects who had been diagnosed with AIA were enrolled in the study. The clinical symptoms and physical characteristics of the subjects were compatible with asthma. Each patient showed airway reversibility, as documented by a positive bronchodilator response of a >15% increase in FEV1 and/or airway hyperreactivity to <10 mg/mL methacholine. The exclusion criteria included duration of asthma of <1 year, acutely exacerbated asthma within 4 weeks, history of brittle asthma, atopy to pollens, parenchymal lung disease apparent on simple chest radiography, and previous use of leukotriene antagonists. This study was approved by the Ethics Committee of Soonchunhyang University Hospital, and informed written consent was obtained from all study subjects prior to enrollment.

Statistical analysis

The data were double-entered into SPSS (ver. 10.0; SPSS Inc, Chicago, IL, USA). The Wilcoxon signed ranks sum test was applied to compare the effects of MLK according to clinical parameters. Comparisons of continuous variables for good and poor responders with asthma were made using the independent samples t-test. Differences in the proportions of patient populations were analyzed by the χ^2 test, with Fisher's exact test when low expected cell counts were encountered. In all analyses, $P<0.05$ was taken to indicate statistical significance.

RESULTS

Clinical parameters of the study subjects

This prospective trial involved 52 patients with AIA. All subjects received 10 mg of MLK before sleep each night for 12 weeks. Six subjects were excluded from the analysis: 2 suffered acute exacerbation following self-withdrawal of inhaled steroid, and four took less than 90% of the scheduled doses of MLK. The compliance rates for medication in the other 46 subjects were above 90%. Thirty-two subjects showed an aspirin-induced de-

cline in FEV1 of less than 15% after the second aspirin challenge (good responders); the decline was greater than 15% in 14 subjects (poor responders, Fig. 1). The mean compliance rate was not significantly different between the good and poor responders (95.5±1.2% and 96.2±1.1%, respectively; $P>0.05$). Thirty subjects had mild asthma and 16 had moderate asthma. Thirty subjects used inhaled steroids. No side effects of MLK treatment that interrupted medication were observed during the study period. The clinical parameters of the subjects are summarized in Table 1.

Comparison of clinical parameters according to the response to MLK

Thirty-two (70%) of the 46 patients who completed the 12-week treatment showed a good response to MLK, with a decline in FEV1 of less than 15% on aspirin challenge after treatment (Table 1). The mean age at diagnosis of aspirin hypersensitivity and the asthma duration were similar between the good and poor responders. The proportions of patients with mild and moderate asthma just before MLK treatment were also comparable between the two groups. The dosages of inhaled steroid were equivalent between the good and poor responders (626±124 μg and 669±102 μg beclomethasone/day, respectively; $P>0.05$). Theophylline was used in combination with inhaled steroid by 3 patients from each group. Nine poor responders

and seven good responders used short-acting inhaled bronchodilators as needed.

The percentage of patients with a history of aspirin hypersensitivity was higher in the poor responders compared with the good responders (57.1 versus 18.8%, respectively; $P=0.014$), and the poor responders had a higher incidence of rhinosinusitis (92.9 versus 65.6%, respectively; $P=0.052$). There were no significant differences between the two groups with respect to the ratio of current to ex-smokers, the frequencies of atopy and nasal polyps, BMI, total IgE, and blood eosinophils (Table 1). There was no difference in FEV1 or FVC between before and after treatment with MLK (Table 1).

Comparison of physiological parameters according to the response to MLK

Before treatment with MLK, the decline in FEV1 following aspirin challenge ranged from 15% to 62% (28.6±1.9%). After 12 weeks of treatment, the decline in FEV1 following aspirin challenge was significantly less, -9% to 51% (10.2±1.7%; $P=0.0001$; Table 2 and Fig. 1A). Nevertheless, 14 subjects (30%) still showed a positive response to aspirin challenge (>15% decline in FEV1) after 12 weeks of treatment with MLK (poor responders), and two subjects showed an increased FEV1 after 12 weeks of treatment, compared with before treatment (Fig. 1A). The decline in FEV1 following aspirin challenge before treat-
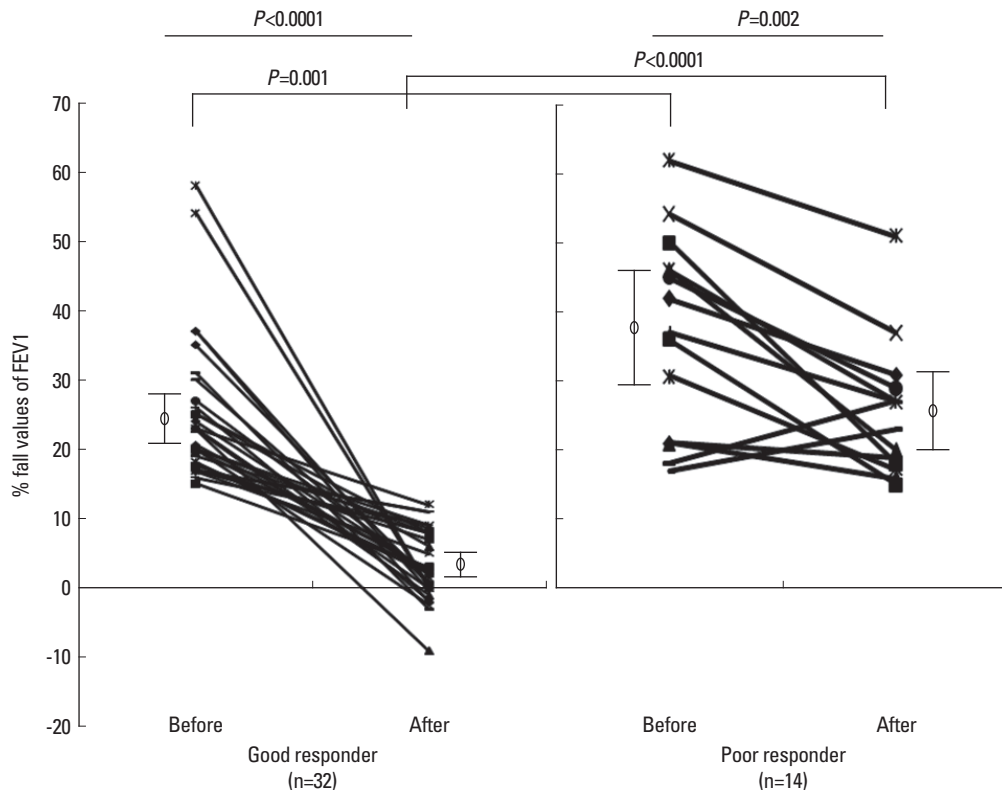

Fig. 1. Change of % fall of FEV1 ratio following aspirin challenge after treatment with Montelukast. Aspirin induced - % fall in FEV1 were measured before and after treatment with daily 10 mg of Montelukast for 12 wk.

ment was different between the good and poor responders (24.7±1.8% versus 37.6±3.8%, respectively; *P*=0.005) (Table 2). Before MLK treatment, the cumulative dose of aspirin required to induce bronchospasm was much lower in the poor responders than in the good responders (860.0±95.3 mg versus 1021.0± 40.8 mg, respectively; *P*<0.05), and the induction time for a positive response was also shorter in the poor responder group (Table 2). The pretreatment PC20 methacholine value was significantly lower in the good responders than in the poor responders (2.95±1.2 mg/mL versus 7.54±3.1 mg/mL, respectively; *P*=0.036). The FEV1 did not differ between the two groups (*P*<0.05) before treatment, and the FEV1 (%, predicted) and

Table 1. Clinical profiles of the study subjects

Clinical profiles	Total	Good responder	Poor responder
No. of subjects	46	32	14
Age of diagnosis (mean (range))	47.2 (18-71)	47.9 (18-71)	45.7 (26-67)
Sex (male/female)	14/32	11/21	3/11
Onset age of asthma (yr) (mean (range))	41.6 (1-68)	42.3 (1-68)	40.1 (16-66)
Duration of asthma (yr) (range)	5.7 (1-28)	5.6 (1-23)	5.7 (1-28)
Asthma severity before treatment with MLK[3] (mild/moderate)	30/16	21/11	9/5
Use of inhaled steroid	30 (65%)	16 (50%)	10 (71%)
Dosage (μg equivalent to beclomethasone/day)	646±113	626±124	669±102
CS/ES/NS[1]	6/6/34	3/5/24	3/1/10
History of AH[2]	14 (30.4%)	6 (18.8%)[†]	8 (57.1%)
History of sinusitis	34 (73.9%)	21 (65.6%)[†]	13 (92.9%)
Nasal polyp	33 (71.7%)	17 (73.9%)	11 (78.6%)
BMI (Kg/m^2) (range)	24.2 (18.9-32.9)	24.0 (18.9-30.1)	24.5 (19.0-32.9)
Total IgE (IU/mL)	342.9±73.6	372.9±100.9	274.2±74.7
Atopy (%)	27 (58.7)	21 (65.6)	6 (42.9)
Blood eosinophil (%)	7.6±0.8	8.1±1.1	6.4±1.0
Blood eosinophil count (/μL)	545.6±72.6	561.9±96.9	508.4±92.3

Good responder: ASA induced rate of FEV1 decline after treatment with MLK <15%; Poor responder: ASA induced rate of FEV1 decline after treatment with MLK >15%; [†]*P* value <0.05 vs. poor responder.
[1] CS/ES/NS, current smoker/ex-smoker/never-smoker; [2] AH, aspirin hypersensitivity; [3] Montelukast treatment, 10 mg/day for 3 mo.

Table 2. Physiologic parameters of the study subjects

Clinical profiles	Total	Good responder	Poor responder
No. of subjects	46	32	14
Before treatment with MLK			
FEV1 (%, predicted)	85.1±2.6	82.4±3.1	91.1±4.9
FVC (%, predicted)	87.2±2.6	86.2±2.3	92.8±4.0
PC20, methacholine (mg/mL)	4.1±1.2	2.95±1.2[†]	7.54±3.1
ASA induced rate of FEV1 decline (%)	28.6±1.9	24.7±1.8[‡]	37.6±3.8
ASA cumulative dose of challenge (mg)	972.0±41.4	1,021.0±40.8[†]	860.0±95.3
Time of positive response	1.6±0.2	1.9±0.2[†]	1.0±0.3
After treatment with MLK[1]			
FEV1 (%, predicted)	86.4±2.8	87.4±3.3	84.0±5.0
FVC (%, predicted)	88.6±2.5	86.2±2.5	86.9±4.1
ASA induced rate of FEV1 decline	10.2±1.7	3.4±0.9[‡]	25.5±2.6
ASA cumulative dose of challenge	968.8±42.1	1,037±34.9[‡]	811.8±104.0
Time of positive response	1.8±0.2	2.0±0.2	1.5±0.3

Good responder: ASA induced rate of FEV1 decline after treatment with MLK <15%; Poor responder: ASA induced rate of FEV1 decline after treatment with MLK >15%; [†]*P* value <0.05 vs. poor responder; [‡]*P* value <0.01 vs. poor responder.
[1] Montelukast treatment, 10 mg/day for 3 mo.

FVC (%, predicted) were comparable in each group.

After 12 weeks of treatment with MLK, the decline in FEV1 following aspirin challenge was significantly lower in the good responders than in the poor responders (3.4±0.9% versus 25.5±2.6%, respectively; P=0.0001). The cumulative dose of aspirin needed to induce bronchospasm was still lower in the poor responders compared with the good responders (811.8±104.0 mg versus 1037.0±34.9 mg, respectively; P<0.05). FEV1 (%, predicted) and FVC (%, predicted) at the second challenge were comparable in the two groups.

DISCUSSION

CYSLTR1 is a G protein-coupled receptor with seven transmembrane domains. It is expressed primarily in airway smooth muscle, eosinophils, macrophages, and splenocytes. Sousa et al. reported that the number of cells expressing CYSLTR1 in the nasal mucosa is significantly higher in cases of AIA with chronic rhinosinusitis than in aspirin-tolerant patients, suggesting that CYSLTR1 overexpression is crucial to the pathogenesis of aspirin hypersensitivity.[4] CysLTs bind to CYSLTR1 with a rank order of potency of LTD4>LTC4>LTE4,[24] and the receptor is antagonized selectively by currently available leukotriene modifiers, including MLK, pranlukast, and zafirlukast.[8,9]

Although CYSLTR1 antagonists are expected to exert protective effects against aspirin-induced asthma in AIA patients, the significance and extent of the effect have remained controversial and inconclusive because of the small study populations and short-term treatment regimens used in previous studies.[16-18] Our findings provide further insight into the protective effect of a CYSLTR1 antagonist against oral aspirin challenge. In AIA patients, the decline in FEV1 following aspirin challenge was markedly decreased after 12 weeks of treatment with MLK, as compared with the values before treatment (Fig. 1A). Nevertheless, 30% of the patients still showed a positive response to aspirin challenge after 12 weeks of MLK treatment, and in two patients, the response to aspirin challenge was greater after MLK treatment than before. This variability in responses has also been observed in a previous study using a sample size of fewer than six subjects.[16] Although our study population was significantly larger, it was still far from being large enough to justify any definitive clinical conclusions. A double-blind, placebo-controlled crossover study with the leukotriene pathway inhibitor zileuton in 40 patients showed a distinct reduction of aspirin-induced bronchospasm.[25] On the other hand, unexpected increases in the frequency of positive aspirin challenge responses in AIA patients taking leukotriene modifier drugs have been reported.[18,26]

We defined the good responder and poor responder groups according to the presence of aspirin-induced bronchospasm after MLK treatment (Fig. 1B). In the present study, poor responsiveness was associated with aspirin hypersensitivity and

sinusitis, but not with age, gender, asthma duration, or the ratio of current to ex-smokers. These data indicate that compared with the good responders, the poor responders might have had a greater response to ingested aspirin. The prevalence of nasal polyps (about 70%) was similar between the two groups, suggesting that the nasal reaction to aspirin ingestion was similar between the groups. One possible alternative explanation for the variability in the response is a difference in awareness among the subjects regarding bronchospasm following aspirin ingestion. To clarify this, we compared the physiological parameters of basal pulmonary function and aspirin-induced bronchospasm.

Before treatment with MLK, the percentage fall in FEV1 following aspirin challenge was greater in the poor responders than in the good responders. In addition, the triggering dose and induction time for aspirin-induced bronchospasm were greater and shorter, respectively, in the poor responders. These observations clearly indicate a greater response to aspirin ingestion in the bronchial trees of the poor responders compared with the good responders. It is not known whether the nasal reactivity was similar to bronchial reactivity, because we did not measure nasal physiology at the same time. Even after treatment with MLK for 12 weeks, the triggering dose for aspirin-induced bronchospasm was not changed from that determined prior to treatment. This suggests that the increased responsiveness of the bronchial tree to aspirin challenge did not change in the poor responders.

The variability in the protective effect of MLK may be attributable to differences in the severity of asthma, as aspirin sensitivity occurs more frequently in cases of severe asthma.[3] In the present study, lung function did not differ between the good and poor responders before or after MLK treatment, suggesting that asthma severity may not be associated with the protective effects of MLK against aspirin-induced bronchospasm. However, we did not include subjects with severe asthma, as they could not be subjected to aspirin challenge. During the study period, the patients were asked to continue taking inhaled steroids at the previous dosage to avoid inhaled steroid withdrawal-associated exacerbation of asthma. One major limitation of the present study was the absence of placebo controls to document the known "spontaneous" variability of asthma, as the spontaneous variability of aspirin hypersensitivity has not been reported.

To search for clinical parameters identifying a poor responder, we compared the BMI, skin test reactivity, total IgE, and peripheral blood eosinophil count between the two groups. None of these parameters were associated with the response. Eosinophils and mast cells show marked infiltration into the bronchial tree and nasal polyps in AIA and are important cell types in aspirin hypersensitivity of the airways.[27,28] Endobronchial aspirin challenge induced a decrease in the number of mast cells that stained for tryptase and an increase in the number of activated

eosinophils, which reflects degranulation of these cell types and an early event associated with aspirin-sensitive reactions in AIA subjects.[29] Elevated levels of eotaxin and eotaxin-2 expression characterize tissue eosinophilia,[30] and these levels are changed after aspirin challenge.[31] In addition, both CYSLT1R and CYSLT2R are expressed on eosinophils, especially during exacerbation of asthma.[32] Leukotriene receptor antagonists are effective in treating AIA, because they inhibit the production of leukotrienes and the degree of eosinophilic inflammation in the airways.[33] Therefore, airway eosinophilia may be a critical marker for responsiveness. However, we did not examine the characteristics of airway inflammation in the present study.

In summary, the ability of a 12-week treatment with MLK to protect against aspirin-induced bronchospasm was evaluated in 46 adult patients with AIA. The protective effects were remarkable, although 30% of the subjects still showed a positive response to aspirin challenge. The presence of aspirin hypersensitivity and sinusitis among the clinical parameters and a greater response to aspirin challenge were associated with a poor response. These observations indicate that the increased responsiveness of the bronchial tree to aspirin challenge does not change in some AIA patients.

ACKNOWLEDGMENTS

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