ORIGINAL ARTICLE

Antitussive Effects of the Leukotriene Receptor Antagonist Montelukast in Patients with Cough Variant Asthma and Atopic Cough

Toshiyuki Kita[1], Masaki Fujimura[2], Haruhiko Ogawa[3], Yasuto Nakatsumi[4], Satoshi Nomura[4], Yoshihisa Ishiura[5], Shigeharu Myou[2] and Shinji Nakao[2]

ABSTRACT

Background: Chronic cough is the only symptom of cough variant asthma (CVA) and atopic cough (AC). Cysteinyl leukotriene receptor antagonists have been shown to be effective in CVA, but there are no reports on their effectiveness in AC. To evaluate the antitussive effect of montelukast, a leukotriene receptor antagonist, in CVA and AC.
Methods: Seventy-five patients with chronic cough received diagnostic bronchodilator therapy with oral clenbuterol hydrochloride for 6 days. Of the 75 patients, 48 and 27 met the simplified diagnostic criteria for CVA and AC, respectively. Patients with CVA were randomly divided into 3 groups: montelukast, clenbuterol, and montelukast plus clenbuterol. Patients with AC were randomly divided into 2 groups: montelukast and placebo. The efficacy of cough treatment was assessed with a subjective cough symptom scale (0 meant "no cough" and 10 denoted "cough as bad as at first visit"). The cough scale, pulmonary function test, and peak expiratory flow rate (PEF) were evaluated before and after 2 weeks of treatment.
Results: In patients with CVA, 2-week treatment with montelukast, clenbuterol, and montelukast plus clenbuterol all significantly decreased cough scores and treatment with montelukast plus clenbuterol was superior to treatment with montelukast alone. In the montelukast plus clenbuterol group, PEF values in the morning and evening significantly increased after 2 weeks compared with values before treatment. In patients with AC, scores on the cough scale did not differ significantly between the montelukast group and the placebo group.
Conclusions: Montelukast was confirmed to suppress chronic non-productive cough in CVA, whereas it was not effective in non-productive cough in AC.

INTRODUCTION

Chronic cough is a common complaint for which patients seek medical attention from primary care physicians.[1] In Japan, cough variant asthma (CVA), atopic cough (AC), and sinobronchial syndrome are the top 3 causes of chronic cough,[2] in contrast to post-nasal drip syndrome, gastro-esophageal reflux disease, and CVA in the United States and the United Kingdom.[3,4]

CVA was originally described by Glauser[5] in 1972 and subsequently by Corrao et al.[6] in 1979 who showed that the cough was responsive to bronchodilator therapy, implying that it was caused by bron-

[1]Department of Respiratory Medicine, National Hospital Organization Kanazawa Medical Center, [2]Respiratory Medicine, Cellular Transplantation Biology, Kanazawa University Graduate School of Medicine, [3]Department of Respiratory Medicine, Ishikawa-Ken Saiseikai Hospital, Toyama, [4]Department of Respiratory Medicine, Kanazawa Municipal Hospital, Ishikawa and [5]Department of Respiratory Medicine, Toyama City Hospital, Toyama, Japan.
Authors' contributions: MF designed this study and revised this paper. HO, YN, SNo, YI, SM and SNa enrolled the patients in this study.
Correspondence: Toshiyuki Kita, MD, Department of Respiratory Medicine, National Hospital Organization Kanazawa Medical Center, 1–1 Shimoishibiki-machi, Kanazawa, Ishikawa 920–8650, Japan.
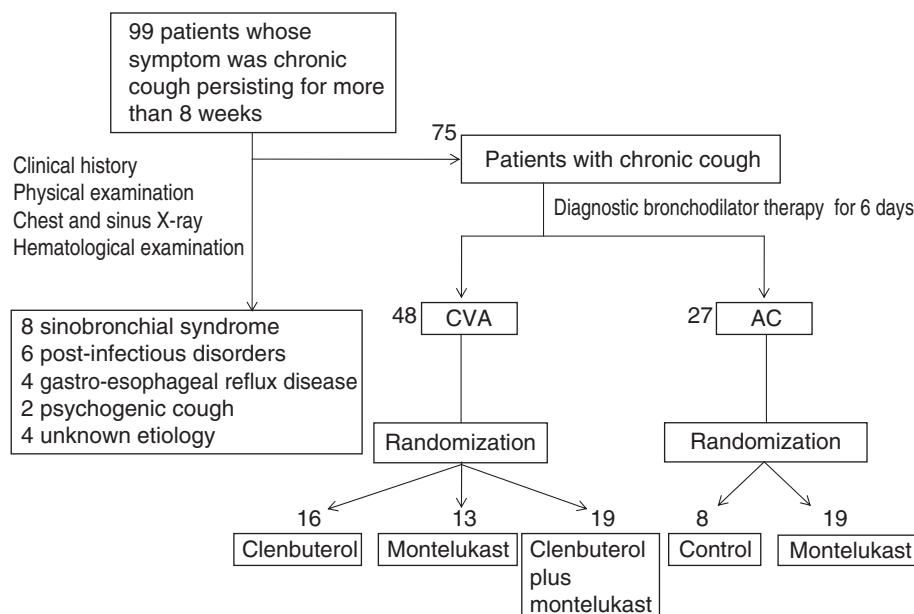Email: naika–k1@kinbyou.hosp.go.jp

Fig. 1 Study protocol.

choconstriction. AC has been defined as an isolated chronic cough resistant to bronchodilator therapy, no variable airflow obstruction, normal airway responsiveness, increased cough reflex sensitivity, and one or more objective indication of atopic constitution as defined by blood or sputum eosinophilia, elevated total or specific immunoglobulin E (IgE) levels, or positive skin tests.[7] Sinobronchial syndrome presenting with productive cough manifests as chronic sinusitis and chronic neutrophilic inflammation of the lower airways, such as chronic bronchitis, diffuse bronchiectasis, and diffuse panbronchiolitis.[8] As is usual in classic asthma, CVA responds to treatment with inhaled bronchodilators[4] and inhaled or systemic corticosteroid therapy.[9] AC is characteristically resistant to treatment with bronchodilators but responds to histamine H1 antagonists and inhaled corticosteroid therapy.[10]

Cysteinyl leukotrienes (LTC4, LTD4, and LTE4) play a major role in the pathogenesis of chronic inflammation in asthma. Selective CysLT1 (LTD4) receptor antagonists have been shown to improve clinical symptoms and pulmonary function in classic asthma.[11] In a randomized, double-blind, placebo-controlled pilot study in 14 patients with CVA, the leukotriene receptor antagonist montelukast was associated with significant improvement in cough.[12] However, the effectiveness of a cysteinyl leukotriene receptor antagonist on cough in AC has not been reported.

Montelukast is a potent and selective antagonist of the cysteinyl leukotriene receptor. The aim of this study was to evaluate the effect of montelukast on cough and pulmonary function in patients with CVA and AC.

METHODS

PATIENTS
Ninety-nine patients, whose sole or predominant respiratory symptom was chronic cough persisting for more than 8 weeks but without wheezing or dyspnea, were enrolled in this study. Participants were from 8 institutes associated with the Kanazawa Asthma Research Group. Participants had no history of asthma. Wheezes or rhonchi were not audible on chest auscultation even at forced expiration. Eosinophil counts in the peripheral blood and sputum, total and specific serum IgE levels, chest and sinus X-ray, bronchial reversibility in terms of increase in forced expiratory volume in 1 second (FEV1) by an inhaled β2 agonist, salbutamol sulfate at a dose of 300 μg (Sultanol™, GlaxoSmithKline, Tokyo, Japan; 100 μg per puff) was examined at the first visit. Patients with other causes of chronic cough, as determined by the investigators based on the clinical history, physical examination, chest and sinus X-ray, examination of total and specific serum IgE levels, sputum eosinophils, and diagnostic treatment procedures recommended by the JRS guidelines[8] were excluded. The study was approved by the ethics committee of each institute, and written informed consent was obtained from all participating patients.

STUDY PROTOCOL (Fig. 1)
After the diagnostic procedure including therapeutic diagnosis, 48 and 27 patients were diagnosed to have CVA and AC, respectively. Bronchodilator therapy which all participating patients received was as fol-

lows: oral clenbuterol hydrochloride (Spiropent™, Teijin Pharma, Tokyo, Japan; 10 μg per tablet, 2 tablets twice daily, 40 μg per day) plus inhaled salbutamol (200 μg, on demand) for 6 days until the day before the second visit (observation period). Efficacy of bronchodilator therapy on cough was assessed as described below, and bronchial responsiveness to methacholine was measured at the second visit (1 week after the first visit). Patients with CVA were randomly divided into 3 treatment groups: the montelukast group (Singulair™, Banyu, Tokyo, Japan; 10 mg per tablet, 1 tablet once daily), clenbuterol group, and montelukast plus clenbuterol group. Patients with AC were randomly divided into 2 treatment groups: the montelukast group and the placebo group. Randomization was performed by each physician based on the patient's chart number. Drugs were administrated to patients with CVA or AC during 2 weeks from the second visit (treatment period). Pulmonary function was measured at the third visit (2 weeks after the second visit). Peak expiratory flow rates (PEFs) in the morning and in the evening were recorded on a "cough diary" every day for 3 weeks (during the 1-week observation period and the 2-week treatment period). Patients recorded cough symptom scale scores 4 times daily (morning, afternoon, evening, and night) and PEF twice daily (morning and evening).

ASSESSMENT OF EFFICACY OF TREATMENT ON COUGH

The efficacy of treatment on cough was assessed with a subjective cough symptom scale (cough scale). During the 1-week observation period and the following 2-week treatment period, all patients recorded their cough scores in a cough diary. Cough was scored on a scale from 0 to 10 points, based on the severity and frequency of their cough for 24 hours at the first visit, after the 1-week observation period, and after the 2-week treatment period. A score of 0 meant "no cough," whereas a score of 10 denoted "cough as bad as at first visit."[13] Based on the diaries, the average of three days (days 5, 6, and 7 from the first visit) was used as the cough scale score for week 1 and that of three days (days 19, 20 and 21 from the first visit) was used as the cough scale score for week 3.

The efficacy of bronchodilator therapy to make a diagnosis of CVA was evaluated on the basis of the change in the cough scale score before and after treatment (Δ cough scale): 10-8 points was regarded as excellent, 7-5 points as good, 4-3 points as fairly good and 2-0 points as unsatisfactory. When Δ cough scale was 3 or more, bronchodilator therapy was judged to be effective.

DIAGNOSIS OF CVA AND AC

CVA and AC as sole causes of chronic cough were diagnosed according to the simplified diagnostic criteria recommended by the Japanese Respiratory Society (JRS).[8] The diagnosis of CVA was made according to the following criteria: (1) isolated chronic nonproductive cough lasting more than 8 weeks; (2) absence of a history of wheezing or dyspnea, and no adventitious lung sounds on physical examination; (3) relief of cough with bronchodilator therapy; and (4) FEV1, forced vital capacity (FVC), and FEV1/FVC ratio within normal limits. The diagnosis of AC was made according to the following criteria[8]: (1) nonproductive cough lasting more than 8 weeks without wheezing or dyspnea; (2) cough resistant to bronchodilator therapy (oral clenbuterol 40 μg/day plus inhaled salbutamol 200 μg at bedtime and on demand); (3) presence of one or more findings indicative of an atopic constitution, including a history and/or complications of allergic disease excluding asthma, peripheral blood eosinophilia (>5% or >400 cells/μL), elevated total serum IgE level (>150 IU/mL), positive specific IgE antibody to aeroallergens and/or induced sputum eosinophilia (≥2.5%); (4) resolution of cough attack with histamine H1 antagonists and/or inhaled and/or oral corticosteroid therapy.

PULMONARY FUNCTION TESTING

Routine pulmonary function was measured at the first visit, the second visit (1 week after the first visit), and the third visit (2 weeks after the second visit). Bronchial reversibility was measured at the first visit, and bronchial responsiveness was determined at the second visit. FVC and FEV1 were measured using a dry wedge spirometer (Chestac 11, Chest, Tokyo, Japan). Spirometry was performed and evaluated according to the American Thoracic Society criteria.[14] To assess bronchial reversibility, spirometry was performed before and 30 minutes after inhalation of 300 μg salbutamol sulfate. PC20, the provocative concentration of methacholine solution causing a 20% fall in FEV1 from the baseline value, was measured as an index of non-specific bronchial responsiveness.[15]

STATISTICAL ANALYSIS

Data values for PC20 were expressed as geometric mean with geometric standard error of the mean (GSEM). Other data values were expressed as mean and SD. The Wilcoxon signed rank test (paired sign test) was used for within-group analyses, and the Mann-Whitney U test was used for comparisons between CVA and AC, and between-group analyses. Data for PC20 were logarithmically transformed. P-values <0.05 were considered statistically significant.

RESULTS

PATIENT CHARACTERISTICS

Diagnostic procedures were completed in 75 of 99 patients with chronic cough who were enrolled in this study. Of the 75 patients, 48 and 27 patients, respec-

Table 1 Patient characteristics

	CVA				AC		
	Clenbuterol	Montelukast	Clenbuterol+ montelukast	Total	Control	Montelukast	Total
Number of subjects	16	13	19	48	8	19	27
Age (yr)	53.1 ± 15.7	43.3 ± 18.2	48.9 ± 17.1	48.8 ± 17.1	40.9 ± 15.4	47.2 ± 17.4	45.3 ± 16.8
Male/female	6/10	6/7	9/10	21/27	2/6	7/12	9/18
Smoking states (+/-)	4/12	5/8	6/13	15/33	1/7	6/13	7/20
Cough duration (weeks)	35.1 ± 67.1	28.5 ± 42.8	31.4 ± 59.7	31.8 ± 57.3	40.5 ± 88.7	37.2 ± 74.0	38.3 ± 77.3
Eosinophils (/μL)	200.2 ± 91.8	176.6 ± 135.7	223.1 ± 201.1	202.4 ± 151.2	165.1 ± 102.9	158.5 ± 98.7	160.5 ± 98.0
Total IgE (IU/mL)	287.8 ± 454.2	120.5 ± 142.4	268.8 ± 757.3	233.1 ± 549.1	173.7 ± 187.6	91.5 ± 130.3	114.5 ± 149.1
FVC, % predicted	109.2 ± 11.5	109.4 ± 12.3	105.9 ± 18.3	108.0 ± 14.6	112.4 ± 21.6	103.3 ± 21.2	105.9 ± 21.4
FEV1, % predicted	101.8 ± 10.4	97.1 ± 32.5	100.4 ± 15.5	100.0 ± 20.0	108.5 ± 16.9	103.3 ± 15.8	104.9 ± 16.0
FEV1/FVC (%)	77.7 ± 9.9	82.2 ± 7.4	81.8 ± 11.2	80.5 ± 9.9	84.3 ± 6.1	83.0 ± 8.8	83.4 ± 8.0
PC20 (mg/mL)	7.66 (6.10)	20.9 (3.80)	8.36 (9.90)	10.89 (6.34)	21.5 (2.70)	14.6 (4.00)	16.2 (3.56)

FVC, forced vital capacity; FEV1, forced expiratory volume in 1 second; PC20, provocative concentration of methacholine causing a 20% fall in FEV1. Data are expressed as mean (SD) except PC20 which is expressed as geometric mean (GSEM) values.
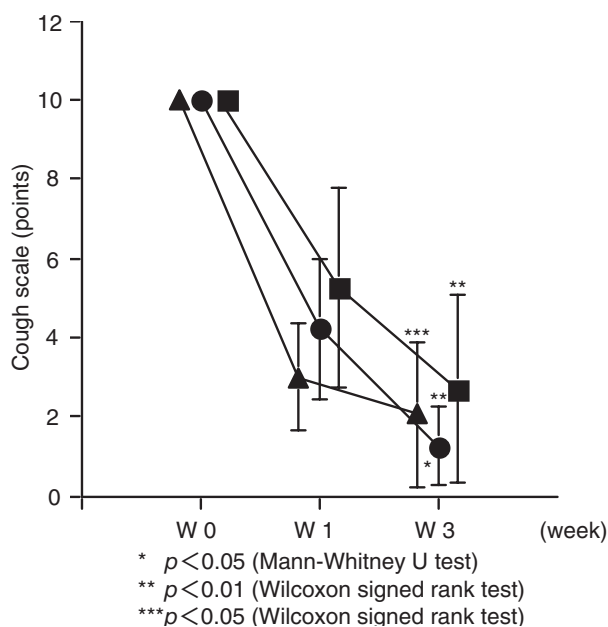

* $p < 0.05$ (Mann-Whitney U test)
** $p < 0.01$ (Wilcoxon signed rank test)
***$p < 0.05$ (Wilcoxon signed rank test)

Fig. 2 Changes in scores of the cough scale in patients with CVA. Filled squares indicate the change in cough scale score in patients treated with montelukast ($n = 13$). Filled triangles indicate the change in the cough scale score in patients treated with clenbuterol ($n = 16$). Filled circles indicate the change in the cough scale score in patients treated with clenbuterol plus montelukast ($n = 19$) . Data are expressed as the mean (SD). Scores on the cough scale in the clenbuterol group (***$p < 0.05$), montelukast group (**$p < 0.01$), and clenbuterol plus montelukast group (**$p < 0.01$) were significantly decreased at week 3 compared with week 1 (Wilcoxon signed rank test). Scores in the clenbuterol plus montelukast group decreased significantly more than scores in the montelukast group (*$p < 0.05$, Mann-Whitney U test).
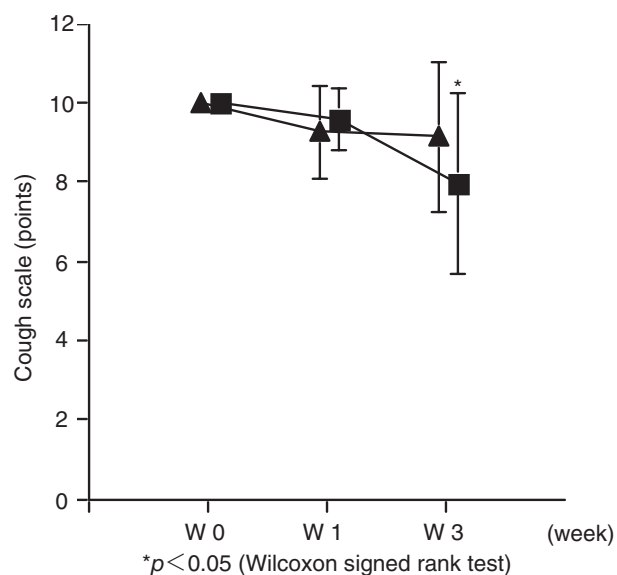

*$p < 0.05$ (Wilcoxon signed rank test)

Fig. 3 Changes in scores of the cough scale in patients with atopic cough (AC). Filled triangles indicate the change in cough scale score in patients treated with placebo ($n = 8$). Filled squares indicate the change in cough scale score in patients treated with montelukast ($n = 19$). Data are expressed as the mean (SD). Scores on the cough scale in the montelukast group (*$p < 0.05$) was significantly decreased at week 3 compared with week 1 (Wilcoxon signed rank test). Scores on the cough scale at week 3 were not significantly different between the placebo and montelukast groups.

tively, met the simplified diagnostic criteria for CVA and AC as the sole causes of chronic cough. Eight patients with sinobronchial syndrome, 6 with post-infectious disorders, 4 with gastro-esophageal reflux disease, 2 with psychogenic cough, and 4 with
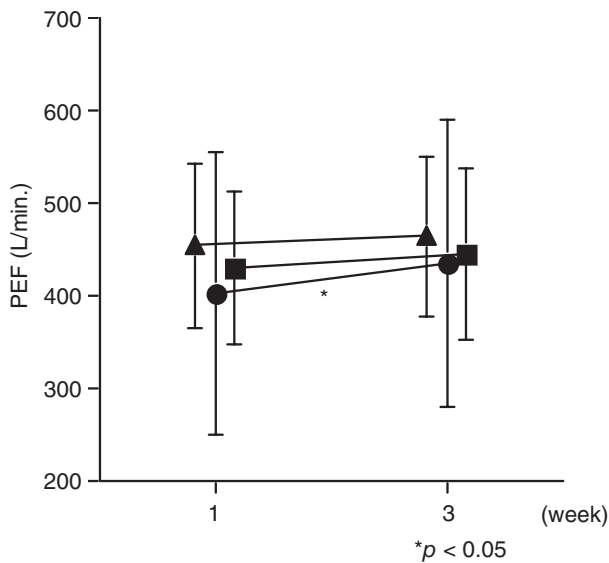
Fig. 4 Changes in morning peak flow rate (PEF) for treatment with montelukast (filled squares) , clenbuterol (filled triangles) , and clenbuterol plus montelukast (filled circles) in patients with CVA. Data are expressed as the mean (SD) . In the montelukast plus clenbuterol group, PEF values in the morning at week 3 were increased significantly ($p < 0.05$) compared with values at week 1.
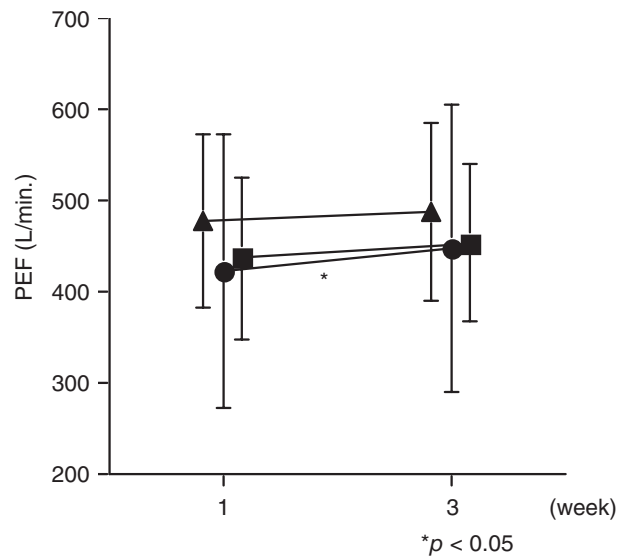

Fig. 5 Changes in evening peak flow rate (PEF) for treatment with montelukast (filled squares), clenbuterol (filled triangles), and clenbuterol plus montelukast (filled circles) in patients with CVA. Data are expressed as the mean (SD). In the montelukast plus clenbuterol group, PEF values in the evening at week 3 were increased significantly ($p < 0.05$) compared with values at week 1.

chronic cough of unknown etiology were excluded from this study. Patient characteristics are summarized in the Table 1.

COUGH SYMPTOMS

In the CVA groups (montelukast, clenbuterol, and montelukast plus clenbuterol), scores on the cough scale at week 1 were decreased significantly (5.2 ± 2.5, 3.0 ± 1.4, 4.2 ± 1.8, respectively) compared with the baseline (week 0), and the scores at week 3 were further decreased significantly (2.7 ± 2.4, 2.1 ± 1.8, 1.3 ± 1.0, respectively) in comparison with each value at week 1 (Fig. 2). Scores on the cough scale in the montelukast plus clenbuterol group were significantly decreased compared with scores in the montelukast group (Fig. 2). In the AC groups (montelukast and placebo), scores on the cough scale at week 1 did not significantly differ from the baseline scores (Fig. 3). In the montelukast group, scores on the cough scale at week 3 (8.0 ± 2.3) were decreased significantly compared with scores at week 1 (9.6 ± 0.8) (Fig. 3), whereas in the placebo group, scores on the cough scale did not differ between week 1 and week 3 (Fig. 3). However, scores on the cough scale with montelukast and placebo at week 1 or week 3 were not significantly different (Fig. 3), suggesting no significant effect of montelukast on the cough in AC.

PEAK EXPIRATORY FLOW RATE (PEF) AND PULMONARY FUNCTION

In the montelukast plus clenbuterol group with CVA, PEF values in the morning and evening at week 3 (433.5 ± 155.0 and 446.9 ± 157.3 L/min, respectively) were increased significantly ($p < 0.05$) compared with values at week 1 (400.3 ± 152.3 and 433.5 ± 155.0 L/min, respectively). In the montelukast group and clenbuterol group with CVA, morning and evening PEF values were not different between week 1 and week 3 (Fig. 4, 5). In the montelukast group and placebo group with AC, PEF values in the morning and evening were not different between week 1 and week 3 (Fig. 6, 7). FVC and FEV1 did not significantly change from week 0 to week 1 or week 3 in the 3 groups with CVA and 2 groups with AC (data not shown).

DISCUSSION

This is the first, randomized, prospective study that showed the ineffectiveness of the CysLT1 receptor antagonist montelukast in patients with AC. The present study also confirmed the effectiveness of montelukast but could not show the significant additive effect of montelukast plus bronchodilator treatment in the patients with CVA.

CVA was originally described by Glauser[5] in 1972 and subsequently by Corrao *et al.*[6] The only presenting symptom of CVA is isolated chronic cough responsive to bronchodilator treatment. Recognition of
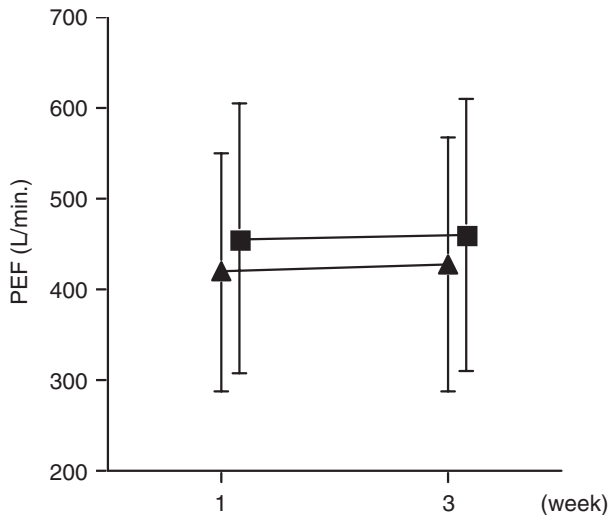
Fig. 6 Changes in morning peak flow rate (PEF) with treatment with montelukast (filled squares) and placebo (filled triangles) in patients with AC. Data are expressed as the mean (SD).

Fig. 7 Changes in evening peak flow rate (PEF) with treatment with montelukast (filled squares) and placebo (filled triangles) in patients with AC. Data are expressed as the mean (SD).
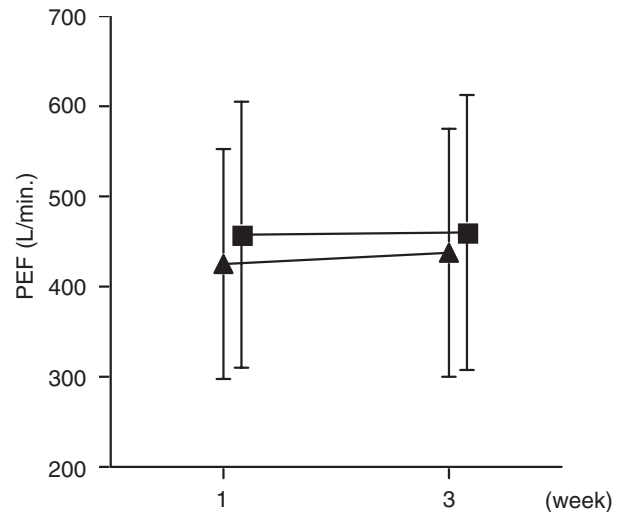
CVA is clinically important because bronchodilator treatment is only effective in CVA. Bronchodilators usually exert no antitussive effect in other causes of isolated chronic cough.[16] Niimi et al.[17] reported that eosinophilic airway inflammation is present by documenting the increased number of eosinophils in bronchoalveolar lavage fluid and biopsied bronchial mucosa and subepithelial-layer thickness occurs in CVA as well as classic asthma.[18,19] Kim et al. reported that sputum eosinophilia is associated with subsequent development of classic asthma, and that children with CVA who developed wheezing demonstrated a further increase in airway responsiveness to methacholine.[19,20] Nearly 30% of CVA patients eventually develop wheezing, sometimes severe enough to require continuous treatment with bronchodilators.[6,21,22] We previously showed that long-term inhaled corticosteroid therapy could prevent typical asthma onset from CVA, and that bronchial hyperresponsiveness was the most important risk factor for typical asthma onset from CVA.[23]

AC is characterized by an atopic background, sputum eosinophilia, cough reflex hypersensitivity, normal pulmonary function, and normal bronchial responsiveness. Cough responds to histamine H1 antagonists[24] and corticosteroids, but not to bronchodilators. Eosinophilic inflammation occurs in central, but not peripheral, airways,[10] and is more prominent in more severe disease.[25] Eosinophilic bronchitis without asthma was first described by Gibson et al.[26] AC shares several features with eosinophilic bronchitis, but may differ by the lack of bronchoalveolar lavage eosinophilia,[10,25] no increased levels of exhaled nitric oxide,[27] and no transformation to typical asthma.[7] Bronchoalveolar lavage eosinophilia,[28,29] increased exhaled nitric oxide,[29,30] and transformation to typical asthma[31] have been shown in eosinophilic bronchitis.

In this study, in patients with CVA, scores on the cough scale decreased after 2 weeks of treatment with montelukast and clenbuterol equally, and scores decreased significantly more with montelukast plus clenbuterol as compared with montelukast alone, but not as compared with clenbuterol alone. The present study failed to show an additive effect of montelukast on bronchodilator therapy in the patients with CVA. The following issues are likely to be responsible for the negative results. The cough symptom was too improved with the 6-day bronchodilator treatment to evaluate the superior efficacy of montelukast plus clenbuterol beyond montelukast or clenbuterol alone. In addition, in the clenbuterol group, scores in the cough scale at week 1 of treatment with clenbuterol were too low to compare with other groups (montelukast alone and montelukast plus clenbuterol). Future study using other protocols is required to elucidate the additive efficacy of montelukast with clenbuterol in CVA. On the other hand, in patients with AC, scores in the cough scale did not differ significantly between the montelukast group and the placebo group.

Dicpinigaitis et al.[13] reported that a 14-day treatment with zafirlukast demonstrated significant improvement in cough in 7 of 8 patients with CVA. Spector et al.[12] reported that mean percentage change from baseline in cough frequency was significantly improved by the second week, and the mean percentage change at the fourth week from baseline was 75.7% for the montelukast group and 20.7% for the placebo group in patients with CVA. These reports are

consistent with the results of our study, demonstrating a significant decrease in scores in the cough scales in the montelukast group.

We planned this study design to confirm the efficacy of montelukast in CVA and used the positive control treatment in this study, because several reports have shown the efficacy of leukotriene antagonists for CVA.[12,13] Thus, we could not evaluate the carry-over effect of clenbuterol in this study. This issue should be evaluated in future studies. Another objective of this study was to examine the efficacy of leukotriene antagonists for AC because the effect of leukotriene antagonists for AC has not been evaluated. In other words, this trial is the first one to elucidate it. Accordingly, we employed the negative placebo treatment group to elucidate the efficacy of montelukast for AC. The reasons why we did not use histamine H1-antagonists as a positive treatment for AC are as follows: 1) the diagnosis of atopic cough was made mainly based on therapeutic diagnostic procedures recommended by the JRS guidelines. Thus, patients with chronic cough, whose cough did not respond to the 6-day bronchodilator therapy, were suspected to have AC and received the test treatment of AC. After this, individual patients were treated according to the JRS guidelines and AC was diagnosed when the cough was completely relieved by histamine H1 antagonists and/or inhaled and/or oral corticosteroids and: 2) we expected that leukotriene antagonists were not effective for AC based on our previous findings using an animal model of AC in which montelukast failed to reduce the increased cough response to inhaled capsaicin 24 hours after antigen challenge in actively sensitized guinea pigs.[32] So, negative control treatment was necessary instead of positive control treatment with histamine H1-antagonists to elucidate the efficacy of montelukast for AC.

Birring et al.[33] measured inflammatory mediator concentrations in induced sputum supernatant from 18 controls and 62 patients with various types of chronic cough, including 20 patients with CVA. Prostaglandin D2 and prostaglandin E2 levels were significantly higher in all the cough groups compared with controls, whereas LTC4, LTD4, and LTE4 levels were significantly higher only in CVA and eosinophilic bronchitis compared with controls. Inhibition of elevated levels of LTC4, LTD4, and LTE4 in patients with CVA and eosinophilic bronchitis by montelukast would be the potential mechanism for the beneficial effects of montelukast.

Our previous study showed that there was a small but significant increase in FEV1 following successful treatment in CVA.[34] Thus, it is likely that a small degree of airway smooth muscle contraction triggers cough in CVA. Reiss et al.[35] demonstrated the ability of montelukast to cause bronchodilatation in asthmatic subjects with baseline airflow limitation. In this study, both morning and evening PEF were increased after treatment with montelukast and clenbuterol in patients with CVA, but not in patients with AC. This finding suggests that the effect of montelukast on cough might result from relief of cysteinyl leukotrienes-mediated smooth muscle contraction in patients with CVA.

In this study, geometric mean values for PC20 were not significantly different between the three groups in patients with CVA. In addition, it has been shown that measurement of PC20 could not predict the efficacy of bronchodilator therapy in patients with chronic cough,[36] and we and other research groups have confirmed the uselessness of PC20 measurement for diagnosis of cough variant asthma. To our knowledge, no reports are available concerning the relationship between severity of cough variant asthma and bronchial hyperresponsiveness. The definition of illness severity for cough variant asthma has not been established. Severity of illness should be graded in the future. In each case, it should be determined which intensity and frequency of coughing or difficulty of treatment is important.

One limitation of our study was that we did not aim to determine the mechanism behind the effects of montelukast in cough. Montelukast has the potential to prevent the release of arachidonic acid and bronchoconstriction induced by inflammatory mediators. The anti-inflammatory effect of montelukast is not stronger than that of inhaled corticosteroids, and its bronchodilator effect is not stronger than β2 agonists.[37,38] In this study, scores on the cough scale with montelukast were not significantly different from scores with placebo in patients with AC, which is consistent with our previous findings using an animal model of AC.[32] These findings suggest that leukotriene receptor antagonists have no benefit in the treatment of AC.

In conclusion, montelukast was confirmed to suppress chronic non-productive cough in patients with CVA and the effect of suppression was equal to clenbuterol. However, montelukast was not effective in patients with AC, strongly suggesting that cysteinyl leukotrienes are not involved in the pathogenesis of AC. Future studies are required to confirm the beneficial effect of montelukast in the treatment of CVA and to clarify the mechanism of its antitussive action.

ACKNOWLEDGEMENTS

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