Clinical, Physiological and Anti-Inflammatory Effect of Montelukast in Patients with Cough Variant Asthma

Masaya Takemura^a Akio Niimi^a Hisako Matsumoto^a Tetsuya Ueda^a
Hirofumi Matsuoka^a Masafumi Yamaguchi^a Makiko Jinnai^a Kazuo Chin^b
Michiaki Mishima^a

Departments of ^aRespiratory Medicine and ^bRespiratory Care and Sleep Control Medicine, Kyoto University, Kyoto, Japan

Key Words

Cough variant asthma • Leukotriene receptor antagonist • Montelukast • Induced sputum • Cysteinyl leukotrienes • Eosinophils • Cough receptor sensitivity

Abstract

Background: Cough variant asthma (CVA) is a phenotype of asthma presenting solely with coughing, characterized by airway hyperresponsiveness, eosinophilic inflammation and a cough response to bronchodilators. Leukotriene receptor antagonists (LTRAs) are antiasthma medications with anti-inflammatory and bronchodilatory properties. Although LTRAs exert antitussive effects in CVA, the mechanisms involved are unknown. **Objectives:** This study aimed to clarify the antitussive mechanisms of LTRAs in CVA patients. **Methods:** We prospectively observed the effect of montelukast (10 mg) daily for 4 weeks in 23 consecutive nonsmoking adults with anti-inflammatory treatment-naïve CVA. We evaluated, before and after treatment, the cough visual analogue scale (VAS), pulmonary function (spirometry and impulse oscillation), methacholine airway responsiveness, cough receptor sensitivity, expressed by the concentration of capsaicin inducing 2 or more (C2) and 5 or more (C5)

coughs, sputum eosinophil counts and levels of inflammatory mediators, including cysteinyl leukotrienes, leukotriene B₄, prostaglandin (PG) D₂, PGE₂, PGF_{2α} and thromboxane B₂. We compared the baseline characteristics of the patients based on the symptomatic response to montelukast, defined as a decrease in the cough VAS of >25% (n = 15) or ≤25% (n = 8). **Results:** Montelukast significantly decreased the cough VAS (p = 0.0008), sputum eosinophil count (p = 0.013) and cough sensitivity (C2: p = 0.007; C5: p = 0.039), whereas pulmonary function, airway responsiveness and sputum mediator levels remained unchanged. Multivariate analysis showed that a better response to montelukast was associated solely with younger age (p = 0.032). **Conclusion:** The antitussive effect of montelukast in CVA may be attributed to the attenuation of eosinophilic inflammation rather than its bronchodilatory properties.

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Introduction

Cough variant asthma (CVA) is a variant form of asthma that presents solely with cough [1] and is one of the most common causes of chronic cough worldwide [2]. Pa-

tients with CVA have mild airway hyperresponsiveness (AHR), as demonstrated by methacholine challenge, and bronchodilators such as inhaled β_2 -agonists and/or oral sustained-release theophyllines are effective against the cough [1]. Modest but variable airflow limitation indicates that bronchial constriction is involved in the mechanism of cough in CVA [3].

Findings in induced sputum, bronchoalveolar lavage and bronchial biopsies have shown that eosinophilic inflammation is involved in CVA as well as in classic asthma with wheezing [4, 5]. Several inflammatory mediators are also implicated in CVA [6, 7]. Prostanoids such as prostaglandin (PG) E_2 , PGF $_{2\alpha}$ and thromboxane (TX) A_2 modulate airway caliber [8, 9] and enhance the cough response to capsaicin [10, 11], which is produced by various cells including eosinophils [12]. Metabolites of lipoxygenase products have recently been identified as ligands of the transient receptor potential vanilloid 1 receptor, also known as the capsaicin receptor [13, 14].

Cysteinyl leukotriene (cys-LT) receptor antagonists (LTRAs) are antiasthma medications that reduce clinical symptoms and improve pulmonary function as well as airway inflammation in patients with classic asthma [15, 16]. An uncontrolled observational study has shown that the LTRA montelukast reduces airway levels of cys-LTs in association with improvements in the quality of life of patients with classic asthma already under treatment with inhaled corticosteroids (ICS) [17]. Although LTRAs exert antitussive effects in CVA [18–20], details of the mechanisms underlying these effects, including anti-inflammatory effects, remain unknown.

The present study examined the effect of montelukast on cough symptoms, pulmonary function, capsaicin cough receptor sensitivity, AHR and sputum inflammatory indices including numbers of eosinophils and levels of inflammatory mediators [cys-LTs, leukotriene B_4 (LTB $_4$), PGD $_2$, PGE $_2$, PGF $_{2\alpha}$ and TXB $_2$] in patients with CVA, in order to investigate its antitussive mechanisms.

Patients and Methods

Study Design

This was a prospective observational study. To elucidate the antitussive mechanism of montelukast, we measured, before and after treatment, cough symptoms, pulmonary function, capsaicin cough receptor sensitivity, AHR and sputum inflammatory indices including eosinophil counts and levels of mediators such as cys-LTs, LTB $_4$, PGD $_2$, PGE $_2$, PGF $_{2\alpha}$ and TXB $_2$ in patients with CVA. The study was approved by the Institutional Review Board of Kyoto University Hospital, and written informed consent was obtained from all participants.

Patients

Twenty-three consecutive patients with CVA (9 males and 14 females; mean age (SD) 46 (16) years) who were referred to the asthma and chronic cough clinic at Kyoto University Hospital were recruited between March 2002 and June 2005. The duration of cough was 3.5 (3.3) years. Nineteen of the patients had never smoked. Four had smoked less than 5 pack-years but had stopped smoking for more than 3 years before entry into the study.

CVA was diagnosed on the basis of chronic cough persisting for >8 weeks, the absence of wheezing or dyspnea, AHR to methacholine and a symptomatic response of coughing to inhaled β_2 -agonists (used as needed or 4 times per day) [1, 4, 21]. Wheezing or rhonchi were not audible on chest auscultation, even with forced expiration. The patients had normal chest radiographs and no history of asthma or other respiratory diseases. No other causes of cough were present, such as gastroesophageal reflux disease or sinobronchial syndrome. None of the patients had ever been administered oral corticosteroids or ICS, antileukotriene drugs, sustained-release theophyllines, TX synthase inhibitors or receptor antagonists, cyclooxygenase inhibitors or angiotensin-converting enzyme inhibitors, or had had an upper respiratory infection within the previous 8 weeks.

Study Protocol

Prebronchodilator pulmonary function was initially determined by impulse oscillometry (IOS) [22] and spirometry, methacholine challenge and sputum induction, in that order. Seven days later, the patients indicated their cough severity during the previous 7 days on a linear visual analogue scale (VAS) on which 0 mm represents no cough and 100 mm the worst cough [23]. Capsaicin cough challenge was performed on the same day, and montelukast (Kipres, Kyorin Pharmaceutical Co. Ltd., Tokyo, Japan; 10 mg/day) was administered in an uncontrolled, open-label fashion for 4 weeks. This is considered long enough to examine the effect of montelukast on cough symptoms and cough receptor hypersensitivity in CVA [18, 19]. After 4 weeks, spirometry, IOS, methacholine challenge and sputum induction were repeated, followed by capsaicin cough challenge 1 week later while the patients were still receiving montelukast.

Sputum Induction and Processing

Sputum was induced and processed as described previously [24, 25]. Briefly, after premedication with inhaled salbutamol, the subjects inhaled hypertonic (3%) saline solution for 15 min, delivered using an ultrasonic nebulizer. The sputum was processed for dispersed cell total and differential counts. Supernatants were stored at -80°C for subsequent mediator measurements. Sputum induction was carried out within 1 h after the methacholine challenge test. Methacholine does not alter the cellular and biochemical constituents of sputum [26].

Measurement of Sputum Levels of Inflammatory Mediators

Concentrations of cys-LTs, LTB $_4$, PGD $_2$ -methoxime, PGE $_2$, PGF $_{2\alpha}$ and TXB $_2$ in the supernatant of induced sputum were measured with sandwich enzyme immunoassay kits (cys-LTs and PGE $_2$: Amersham Biosciences Corp., N.J., USA; LTB $_4$, PGD $_2$ -methoxime, PGF $_{2\alpha}$ and TXB $_2$: Cayman Chemical, Ann Arbor, Mich., USA) according to the manufacturers' instructions. Duplicate measurements were averaged for analysis. Because PGD $_2$ and TXA $_2$ are both relatively unstable, we measured PGD $_2$ -methox-

ime and TXB₂, which are stable derivatives of PGD₂ and TXA₂, respectively [7]. The detection limit of each mediator was 10, 13, 3.1, 40, 8 and 11 pg/ml for cys-LTs, LTB₄, PGD₂-methoxime, PGE₂, PGF_{2α} and TXB₂, respectively.

Pulmonary Function

We conducted IOS using an MS-IOS (Erich Jaeger, Hoechberg, Germany) as described elsewhere [25, 27–29] and according to standard recommendations [30]. We measured R5 and R20 as indices of total and proximal airway resistance, respectively, and considered the difference between them (R5 – R20) a surrogate marker of small airway resistance. Reactance at 5 Hz (X5) was also measured as an index of peripheral airway abnormalities [22, 25, 29, 30]. IOS is a simple and noninvasive method of assessing pulmonary function without forced maneuvers, and the indices respond to therapeutic intervention or correlate with pathophysiological indices more sensitively than those of spirometry [25, 27–29, 31].

The spirometric indices forced expiratory volume in 1 s (FEV₁) and mid-forced expiratory flow (FEF_{25–75%}), as well as the reversibility of FEV₁ with a β-agonist, were measured according to recent recommendations [32].

Capsaicin Cough Challenge

Capsaicin cough receptor sensitivity was measured as described previously with slight modifications [33]. Briefly, 10 doubling concentrations of capsaicin (0.61–312.5 μM) were inhaled during tidal breathing until 2 or more coughs and 5 or more coughs were induced (cough thresholds C2 and C5, respectively). The patients inhaled a saline control followed by progressively increasing concentrations of capsaicin. Each 15-second capsaicin inhalation was interspersed with saline inhalation for 45 s as a blind.

Methacholine AHR

AHR was examined by continuous methacholine inhalation with simultaneous measurement of respiratory resistance (Rrs; cm H₂O/l/s) (Astograph; Chest, Tokyo, Japan) [34]. Briefly, two-fold increasing concentrations of methacholine solution in 10 dose steps (49–25,000 μg/ml) were prepared. They were inhaled during tidal breathing from nebulizers with an output of 0.15 ml/min. After recording the baseline Rrs during inhalation of physiologic saline for 1 min, methacholine was inhaled sequentially, starting from the lowest concentration, at 1-min intervals. The cumulative dose of inhaled methacholine at the inflection point at which Rrs begins to increase (Dmin) was used as the index of airway sensitivity. This variable was measured in terms of a unit defined as 1-min inhalation of 1 mg/ml methacholine. Inhalation of methacholine was continued until Rrs reached twice the baseline value. The slope of the methacholine-Rrs dose-response curve (SRrs) was used as the measure of airway reactivity. The total cumulative dose of methacholine after inhalation of the highest dose was 50 units.

This method was developed and established by Takishima et al. [34] and further validated by our group [35].

Response to Montelukast

Patients were assigned to groups according to their response to montelukast. A better symptomatic response to montelukast was arbitrarily defined as a >25% decrease in VAS (ΔVAS >25%).

Table 1. Changes in 23 patients treated with montelukast for 4 weeks

	Montelukast treatment		p value
	before	after	
Cough VAS, mm	40.3 (22.1)	19.3 (14.8)	0.0008
FEV ₁ , % predicted	103 (13)	106 (16)	0.13
FEF _{25–75%} , % predicted	96 (30)	101 (32)	0.65
R5, kPa/l/s	0.31 (0.10)	0.33 (0.11)	0.89
R20, kPa/l/s	0.27 (0.07)	0.28 (0.07)	0.96
R5 – R20, kPa/l/s	0.04 (0.04)	0.05 (0.05)	0.42
X5, kPa/l/s	–0.12 (0.06)	–0.11 (0.06)	0.60
log C2, μM	0.49 (0.72)	0.77 (0.75)	0.007
log C5, μM	0.79 (0.75)	0.98 (0.74)	0.039
log Dmin, units	0.32 (1.08)	0.70 (0.58)	0.51
SRrs, cm H ₂ O/l/s/min	2.08 (1.64)	1.93 (1.48)	0.65
Sputum indices			
Eosinophils, × 10 ⁵ /g	1.23 (3.36)	0.55 (1.25)	0.013
cys-LTs, ng/ml	18.4 (15.8)	12.8 (14.7)	0.50
LTB ₄ , ng/ml	5.24 (6.37)	4.86 (6.94)	0.96
PGD ₂ , ng/ml	0.14 (0.29)	0.05 (0.05)	0.21
PGE ₂ , ng/ml	1.25 (1.11)	1.11 (0.91)	0.69
PGF _{2α} , ng/ml	0.83 (0.62)	0.74 (0.49)	0.80
TXB ₂ , ng/ml	1.94 (1.79)	1.58 (1.41)	0.59
Data are means (SD).			

Baseline characteristics, including physiological and inflammatory indices, of these patients were compared with those of the remaining patients (ΔVAS ≤25%).

Statistical Analysis

Values are expressed as means (SD). Changes in symptoms after treatment with montelukast were analyzed using the Wilcoxon signed-rank test. Subgroups classified according to the response to montelukast were compared by univariate analysis using the Mann-Whitney U test or Fisher's exact probability test. Independent factors associated with the response to treatment were tested using logistic regression analysis. p values of <0.05 were considered statistically significant.

Results

Effect of Montelukast

Table 1 and figure 1 show changes in symptoms, physiological indices and inflammatory parameters of sputum before and after treatment with montelukast. The cough VAS improved from 40.3 (22.1) to 19.3 (14.8) mm after 4 weeks (p = 0.008), with a mean (SD) improvement rate of 52.2% (33.0). With respect to cough receptor sensitivity, C2 increased in 13 of the 23 patients (57%) after

Fig. 1. Effects of montelukast for 4 weeks on cough VAS (a), log C2 (b), log C5 (c) and sputum eosinophil counts (d) in patients with CVA.

treatment but did not change in 8 and decreased in 2, while log C2 improved from 0.49 (0.72) to 0.77 (0.75) μM ($p = 0.007$). Also, C5 increased in 11 patients (48%) but was unchanged in 9 and decreased in 3; log C5 improved from 0.79 (0.75) to 0.98 (0.74) μM ($p = 0.039$). Adequate pairs of sputum samples were collected from 17 of the 23 patients before and after treatment. The number of sputum eosinophils decreased with treatment from 1.23 (3.36) to 0.55 (1.25) $\times 10^5/\text{g}$ ($p = 0.013$). However, spirometric and IOS indices, airway sensitivity and reactivity, and sputum levels of cys-LTs, LTB₄, PGD₂, PGE₂, PGF_{2 α} and TXB₂ did not change significantly (table 1).

Baseline Clinical Characteristics according to Response to Montelukast

The symptomatic response to montelukast was better ($\Delta\text{VAS} > 25\%$) in 15 of the 23 patients (65%). The results

Table 2. Baseline characteristics of patient subgroups according to montelukast response

	Response to montelukast		p value
	$\Delta\text{VAS} > 25\%$	$\Delta\text{VAS} \leq 25\%$	
Male/female, n	5/10	4/4	0.66
Age, years	42 (13)	56 (13)	0.026
Disease duration, years	3.6 (4.0)	3.2 (2.0)	0.56
Nonsmokers/ex-smokers, n	13/2	6/2	0.59
Atopy/nonatopy ^a , n	9/6	4/4	0.68
FEV ₁ , % predicted	100 (12)	110 (12)	0.053
FEF _{25–75%} , % predicted	91 (29)	104 (31)	0.20
FEV ₁ β_2 reversibility, %	4.4 (6.1)	2.1 (3.6)	0.24
R5, kPa/l/s	0.31 (0.11)	0.31 (0.08)	0.61
R20, kPa/l/s	0.26 (0.08)	0.27 (0.07)	0.75
R5 – R20, kPa/l/s	0.04 (0.04)	0.04 (0.03)	0.97
X5, kPa/l/s	–0.14 (0.07)	–0.09 (0.03)	0.14
log C2, μM	0.3 (0.5)	0.8 (0.9)	0.19
log C5, μM	0.8 (0.7)	1.0 (0.9)	0.77
log Dmin, units	0.047 (0.93)	0.77 (1.2)	0.030
SRrs, cm H ₂ O/l/s/min	2.26 (1.94)	1.71 (0.58)	0.54
Sputum indices (n = 9)		(n = 8)	
Eosinophils, $\times 10^5/\text{g}$	0.54 (0.73)	2.00 (4.9)	0.81
cys-LTs, ng/ml	17.6 (16.8)	19.6 (15.5)	0.85
LTB ₄ , ng/ml	3.55 (3.76)	7.14 (8.23)	0.56
PGD ₂ , ng/ml	0.21 (0.40)	0.06 (0.05)	0.44
PGE ₂ , ng/ml	1.16 (1.12)	1.37 (1.16)	0.70
PGF _{2α} , ng/ml	0.85 (0.70)	0.80 (0.55)	>0.99
TXB ₂ , ng/ml	2.18 (2.10)	1.60 (1.32)	0.77

Data are means (SD).

^a Atopy is defined as the presence of at least one positive specific IgE response against eight common allergens [61].

of the univariate analysis showed that the better responders were significantly younger ($p = 0.026$) and more sensitive to methacholine ($p = 0.030$) than those with $\Delta\text{VAS} \leq 25\%$ (table 2). Other indices, including IOS and spirometry, log C5, airway reactivity, sputum eosinophil count and sputum mediator levels including that of cys-LTs, did not differ between the subgroups. Montelukast responses, assessed as the percentage change in physiological indices (FEV₁, FEF_{25–75%}, R5, R20, R5 – R20, X5, log C2, log C5, log Dmin or SRrs) and the number of sputum eosinophils, also did not differ between subgroups (data not shown). Multiple linear regression analysis including age and log Dmin identified younger age as the sole predictor of a better responsiveness to montelukast (table 3).

An analysis of 17 patients who had adequate pairs of sputum samples before and after treatment revealed no

Table 3. Multiple regression model for better response to montelukast

	Odds ratio	p value
Age	0.89 (0.78–0.99)	0.032
log Dmin	0.26 (0.063–1.08)	0.064

Values in parentheses represent 95% confidence intervals.

significant correlations among percentage changes in VAS, sputum eosinophils, log C2 and log C5 (data not shown). In addition, percentage changes in the sputum eosinophil count were unrelated to those in sputum mediator levels (data not shown). In all of the 23 subjects, percentage changes in VAS were also unrelated to those in C2 or C5 (data not shown).

Discussion

We investigated the clinical, physiological and anti-inflammatory effects of montelukast in patients with CVA. Effects on the cough VAS and cough receptor sensitivity were confirmed as in other studies [18, 19]. We also discovered a significant decrease in sputum eosinophil count, although IOS and spirometry indices remained unchanged.

Ample evidence supports the effectiveness of LTRAs against classic asthma [15, 16, 36], and their value against CVA has also been reported [18–20, 37]. A placebo-controlled crossover study found that 2 weeks of treatment with zafirlukast significantly improved cough scores and capsaicin cough receptor sensitivity in 8 patients with CVA, while FEV₁ values remained unchanged [18]. Four weeks of treatment with montelukast improved subjective and objective measures of cough frequency and scores on the Asthma Quality of Life questionnaire without a concomitant change in FEV₁ in 8 patients with CVA, as compared with 6 who received a placebo [19]. However, the antitussive mechanisms of the LTRAs were not examined in these small studies, except for one analysis of bronchial tissue from a subset of patients (n = 13), which showed that responders to montelukast had increased numbers of CD63-positive cells (activated mast cells) compared with nonresponders [37].

Airflow limitation is usually minimal in CVA, as it was in our patients, while being involved in the pathogenesis of cough in CVA that is attenuated by bronchodila-

tors [1, 3, 4, 21]. Airway caliber changes that may be missed by spirometry can be sensitively detected by IOS [22, 25, 27–29, 31], but we found no significant changes in indices of IOS, nor in indices of spirometry, after treatment with montelukast, which was consistent with previous findings [18, 19]. The antitussive effect of montelukast in CVA may thus be attributable to its anti-inflammatory properties that attenuate eosinophilic inflammation rather than to bronchodilation.

Tussive inflammatory mediators, which may activate afferent sensory nerve endings, have been implicated in the pathogenesis of cough [7, 38, 39]. Inhalation studies in healthy individuals [9, 10] and inhibition studies of the specific antagonists of inflammatory mediators in asthmatic patients [11] have shown that prostanoids such as PGE₂, PGF_{2α} and TXA₂ are associated with the cough reflex. A recent in vitro study revealed that the metabolites of lipoxygenase products such as 12- and 15-(S)-hydroperoxyeicosatetraenoic acids, 5- and 15-(S)-hydroxyeicosatetraenoic acids and LTB₄ might be ligands for transient receptor potential vanilloid 1 receptors [13]. The expression of such receptors is increased in the airways of patients with chronic cough, including those with CVA [40], indicating their involvement in cough hypersensitivity [14]. However, evidence supporting direct tussive effects of cys-LTs on ‘cough receptors’ is scarce.

Montelukast decreases cys-LT levels in the exhaled breath of patients with classic asthma [17, 41]. To our knowledge, this is the first study to investigate the detailed anti-inflammatory effect of an LTRA in CVA, and we revealed that montelukast significantly decreased sputum eosinophils as well as the cough VAS and capsaicin sensitivity but did not affect sputum levels of cys-LTs, LTB₄, PGD₂, PGE₂, PGF_{2α} and TXB₂. Since eosinophils are a source of various prostanoids [12] and cys-LTs [42], we postulated that montelukast exerts antitussive effects by attenuating eosinophilic inflammation with a resultant fall in some prostanoid and cys-LT levels in CVA. However, our results disproved this notion. Percentage changes in sputum eosinophils were unrelated to those of sputum levels of mediators, including cys-LTs.

With respect to cys-LTs, the discrepancy of the results between the previous breath condensate studies conducted in classic asthma patients presenting with wheezing [17, 41] and our sputum study of CVA patients may have derived from possible pathophysiological differences between CVA and classic asthma. In CVA and the related condition eosinophilic bronchitis, activation of

mast cells has been indicated by the increased sputum levels of the mast cell-derived tussive mediators histamine and PGD₂ [7], while this is not a feature of classic asthma [43]. A recent bronchial biopsy study has also implicated the activation of mast cells in the pathophysiology of CVA [37]. Such evidence may suggest that mast cells rather than eosinophils are a relatively more important source of cys-LTs in patients with CVA as compared with those with classic asthma. As for other mediators measured in this study, major cellular sources are cells other than eosinophils (e.g. mast cells for PGD₂, alveolar macrophages for PGE₂ and neutrophils for LTB₄) [44] which are poorly responsive to LTRAs, unlike eosinophils. This may explain why our mechanistic hypothesis was not verified. Since ICS, which are potent inhibitors of eosinophilic inflammation, do not alter cough sensitivity in CVA [45], whereas LTRAs do, as we and others [18] have shown, LTRAs might exert a different antitussive mechanism from ICS.

In a study by Birring et al. [7], sputum mediator levels were measured in 18 healthy subjects and in three subgroups of chronic cough patients (CVA or eosinophilic bronchitis, *n* = 20; various causes of nonasthmatic cough, *n* = 20; idiopathic cough, *n* = 22). Levels of PGD₂ and PGE₂ were significantly higher in all cough subgroups compared with controls, and histamine levels were also increased in the CVA and eosinophilic bronchitis and idiopathic cough subgroups, whereas cys-LT levels were increased only in the CVA and eosinophilic bronchitis subgroup. These results indicate that cys-LTs are specifically involved in cough associated with eosinophilic airway disorders, whereas PGD₂, PGE₂ and histamine are universally involved in the common mechanism of cough.

One possible mechanism for the association of cys-LTs with cough in CVA is via the tussive mediator substance P. The expression of substance P in the airway epithelium is increased in CVA patients compared with classic asthma patients and healthy subjects, both of whom express similar amounts of substance P [46]. We have also reported that plasma levels of substance P are elevated in patients with CVA and cough-predominant asthma as compared with healthy subjects [47]. cys-LTs induce the release of substance P through the stimulation of airway afferent nerve fibers [48], and LTRAs inhibit such release [48, 49]. Evidence that LTRAs attenuate cough receptor sensitivity in CVA [18] but not classic asthma [50] might be consistent with this hypothesis, but the details remain to be clarified.

The effect of LTRAs in classic asthma is variable. This has been attributed to the effects of genetics [51], smoking [52] and also age. Symptoms and lung function respond better to zafirlukast in patients aged <65 years than in older patients [53]. The effect of zafirlukast is better among patients aged <50 years [54, 55]. Our results are consistent with these findings, but the mechanisms involved are unknown. Sputum levels of mediators mainly derived from mast cells, such as PGD₂, were not increased in our patients with better responses to montelukast, which contradicts the suggested hypothesis [37].

Some limitations of our study should be noted. We arbitrarily defined a better response to montelukast as a >25% decrease of VAS based on our clinical experience, not on evidence. The European Respiratory Society guidelines on the assessment of cough recommend using the cough VAS for assessment of chronic cough severity [23]. Actually, there is evidence that the cough VAS score is highly reproducible [56] and responsive to intervention [57] when used as an outcome measure in clinical studies of chronic cough. However, the minimal change in VAS needed to judge the efficacy of intervention remains to be determined. The British Thoracic Society guidelines of cough have defined the minimal significant improvement of cough as a change in VAS of 15 mm [58]. However, this is not even based on evidence. We readily admit that future validation studies are essential for this issue. The lack of a control group is another limitation of our study. This might have affected the precise evaluation of treatment effects. However, a placebo effect of montelukast upon sputum eosinophils and coughing that had persisted for an average of 3.5 years seems unlikely. We believe that the observed efficacy of montelukast on the cough VAS, cough sensitivity and sputum eosinophilia but not on pulmonary function measures is relevant in the absence of controls. Moreover, this short-term study could not investigate the effect of treatment on the long-term consequences of disease such as the development of irreversible airflow obstruction [1], airway remodeling [5, 59] and progression to classic asthma, which might be preventable by ICS [60].

In conclusion, we found that the cough VAS, sputum eosinophil counts and cough sensitivity significantly improved in CVA patients treated with montelukast for 4 weeks, while pulmonary function did not change. The antitussive effect of montelukast in CVA might be attributable to its anti-inflammatory ability rather than bronchodilation. However, the detailed mechanisms remain to be clarified by future controlled studies.

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