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Original Paper

The effectiveness of treating patients with recurrent cough variant asthma with leukotriene receptor antagonist montelukast sodium

—— Clinical parameters concerned with therapeutic responsiveness ——

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Abstract

There have been only a few reports regarding the effectiveness of leukotriene receptor antagonist (LTRA) in the treatment of patients with cough variant asthma (CVA).

Methods: The present research in patients (9 males, 17 females; age 59±23 yr) with recurrent CVA was performed to investigate the effectiveness of a 2-week course of the LTRA montelukast sodium (MT) based on clinical use of a cough score (CS). Secondly we performed a sub-analysis of clinical parameters for CS, age, and gender in the condition-matched cases drawn from the total cases.

Results: Of the 26 cases studied, the course of MT was effective in 19 cases (rate of responsiveness, 73%; 11 cases, good response; 8 cases, moderate response) and induced no response in 7 cases. MT improved the rate of CS by 37±33%, from 4.7 ±2.2 to 3.2±2.5 points ($P<0.001$). The improvement rate of CS was significantly related to the CS before treatment ($r=-0.47$, $P=0.02$). The therapeutic responsiveness was significantly higher in low score cases than high score cases ($P=0.03$). Cough severity was assumed to be a parameter of therapeutic responsiveness. Significant differences for therapeutic responsiveness were not observed between non elderly and elderly patients, nor between males and females.

Conclusions: MT is sufficiently effective in patients with recurrent CVA. In terms of drug compliance, the understanding of inhaled therapy, and complications in the elderly, elderly cases are considered to be active indications for MT therapy. The present study suggests the recommended concomitance of β_2-agonist or inhaled (or oral) corticosteroids with MT in severe cases at the early stage of treatment.

Key words: Cough variant asthma, Montelukast sodium, Leukotriene receptor antagonist, The elderly, Gender

Introduction

Cough is a common clinical symptom not only in respiratory clinics, but also in general practice. The causes of chronic persistent cough are diverse, and diagnosing them and prescribing therapy can be difficult. In 1979, Corrao et al. reported on six subjects with a variant form of bronchial asthma who complained of chronic cough without

wheezing or dyspnea, and these conditions have been recently recognized as a common cause of chronic cough known as cough variant asthma (CVA). In patients with chronic cough, the causes are assumed to be one or more (21～26%) of the following: bronchial asthma, CVA, eosinophilic bronchitis, sinusitis with postnasal drip, or gastro-esophageal reflux disease et al. (Irwin et al., 1990 ; Yamasaki et al., 2003). In our experience, CVA is the most common cause (27%) of isolated chronic cough in outpatients (Yamasaki et al., 2003). Patients with CVA reveal normal spirometry but airway hyperresponsiveness (AHR) when examined with methacholine. With regard to therapy, bronchodilators are effective and can be used for clinical diagnosis.

It is assumed that CVA progresses to typical asthma in nearly 30% of cases. CVA is thought to be one of the most important conditions that shift to bronchial asthma. The leukotriene receptor antagonist (LTRA) has been recently positioned as an important drug in bronchial asthma. However, there have been only a few reports of the effectiveness of LTRA in the treatment of patients with CVA, and there have been particularly few studies of montelukast sodium (MT), an LTRA characterized by its comparatively immediate effects and once-daily use in treatment. It has been reported that MT is effective in the treatment of patients with CVA, including non recurrent cases (Yamasaki, 2003). However, there is no evidence regarding whether LTRA is as effective in the elderly as in the non elderly, and regarding what clinical parameters influence therapeutic effectiveness.

In the present study, we examined whether MT is effective for use in cases with recurrent CVA in order to obtain a heightened diagnostic accuracy, and performed a sub-analysis of the clinical parameters with regard to therapeutic responsiveness.

Methods

Study Subjects

Twenty-six cases diagnosed as CVA were studied in the following study protocol (9 males, 17 females ; age 59±23 yr). These patients were referred to our Internal Medicine clinic complaining of chronic cough between November, 2001 and December, 2003. The patients granted informed consent and were enrolled in this therapeutic protocol.

Methods

(1) Diagnosis of CVA

The cases manifesting with non productive cough persisting for more than 4 weeks as their sole respiratory symptom were tested using the following combined examinations. Organic disorders were excluded, and cases with a previous history of child bronchial asthma, chest disease, upper respiratory infection within the preceding 8 weeks, or taking angiotensin-converting enzyme inhibitors were excluded. The tests performed included the following: imaging tests including chest X-ray and spirometric measurement in all cases, and chest CT, sinus MRI, and gastroendoscopy with the proton pump inhibitor test if necessary ; laboratory tests including hematological tests with inflammatory reaction and total IgE in total cases, serum antibody for mycoplasma, chlamydia pneumoniae and pertussis, culture of sputum, and the induced sputum test if necessary. The non organic recurrent cases were treated with β_2-adrenoreceptor agonist (β_2-agonist), tulobuterol tape at a dosage of 2mg once daily, for a week. When the cough symptoms were reduced to less than 50%, CVA was diagnosed clinically because AHR examined with methacholine does not finally determine the diagnosis of CVA, and a chronic cough sufficiently responsive to bronchodilators can only be CVA (Fujimura et al., 1994 ; Irwin et al., 1997). In the present study, we only selected the recurrent cases that sufficiently responded to β_2-agonist in order to obtain an accurate diagnosis.

(2) Evaluation of Cough Severity

A subjective assessment of cough symptom severity was recorded for each patient using the following previously reported cough scores (CS) (Yamasaki, 2003). The day was divided into 3 time zones, from 6 : 00 to 14 : 00, from 14 : 00 to 22 : 00, and from 22 : 00 to 6 : 00 the next morning, and in each time zone, the cough symptom was graded as described below, and the CS, ranging from 0 to 9 points, was determined as the sum of the scores of all of the time zones. The grade of the time zone was defined semi-quantitatively as follows : 0, no symptoms ; 1, sometimes coughing and/or waking up less than two times per night ; 2, often coughing and/or waking up more than three times ; 3, frequently coughing so that it was difficult to talk or telephone, and/or hav-

ing sleep continuously disturbed.

(3) Study Protocol of MT administration

The subjects diagnosed as CVA were treated with MT 10 mg once daily for 2 weeks, and we classified cases in which the CS improved over 50% as a good response (effective), cases without changes in CS as no response (ineffective), and the rest as a moderate response (slightly effective). If the CS did not decrease to less than 50% of the baseline during 2 weeks of MT administration, tulobuterol tape at a dosage of 2 mg once daily and then if necessary tulobuterol tape plus inhaled (or oral) corticosteroid (beclometasone dipropionate) at a dosage of more than 600 μg daily were added.

(4) Evaluation Items and Statistical Analysis

The effectiveness of the drug was judged after a 2-week administration of MT using CS. The improvement rate of CS (i-CS) was calculated; CS before MT — CS after MT/CS before MT $\times$ 100 (%). The cases were divided according to the following clinical parameters, and the therapeutic effectiveness was analyzed using i-CS in the condition-matched cases drawn from the total cases; ①high score cases (CS $\geq$ 6 points) versus low score cases (CS $\leq$ 5 points), ②the non elderly cases (<65 yr) versus the elderly cases ($\geq$65 yr), ③male cases versus female cases.

Statistical analysis was carried out as follows. Improvement of the CS was compared by Wilcoxon signed-ranks test in the total cases. The efficacy was compared by Mann-Whitney U test in the condition-matched cases of ①, ②, ③. A p value of less than 0.05 was considered to indicate statistical significance.

Results

The results of the above research are shown in Table 1. No cases worsened and showed adverse effects. Sixteen cases (62%) showed atopic factor-related data, including allergic rhinitis, allergic dermatitis, increases in eosinophilic levels in peripheral blood, or an increase in total IgE. Of the 26 cases studied, 11 cases (42%) showed a good response (effective), 8 cases (31%) a moderate response, and 7 cases (27%) no response (ineffective), as shown in Fig. 1. In the total cases, the rate of responsiveness achieved to 73%. The CS before MT treatment was negatively correlated with i-CS; r=−0.47, P=0.02: Pearson's correlation coefficient (details not shown here). Since chronic cough is the only sign or symptom and is the determinant of QOL in patients with CVA, CS is assumed to reflect the severity of CVA. The results of condition-matched analysis in clinical parameters are shown in Table 1 and Fig. 1. The therapeutic responsiveness was significantly higher in low score cases than high score cases (P=0.03). No significant differences in therapeutic responsiveness were

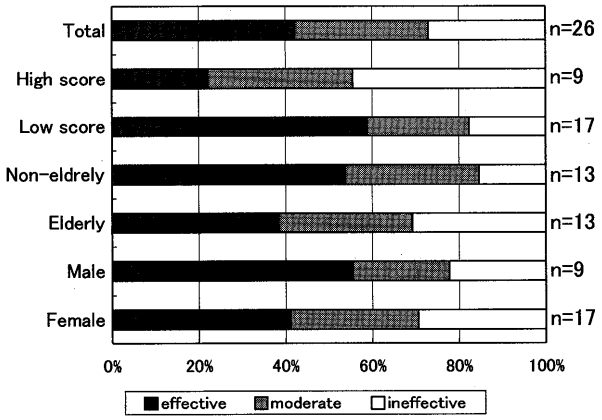

Fig. 1 Effectiveness of Montelukast Sodium

Table 1 Summery of cases with recurrent cough variant asthma

	n	male/female	age	CS (before)	CS (after)	i-CS (%)	atopic factor
1) Total cases	26	9/17	59±23	4.7±2.2	3.2±2.5	37±33	16
2) age and gender-matched (n=25)							
High Score	10	3/7	60±15	7.1±1.3	5.8±2.2	19±24	6
Low Score	15	5/10	60±20	3.1±0.9	1.6±1.0	48±34	10
3) score and gender-matched (n=20)							
Non-elderly	10	3/7	41±21	4.4±1.6	2.4±2.0	50±34	8
Elderly	10	3/7	74±10	4.3±2.3	3.0±2.4	34±32	5
4) age and score-matched (n=19)							
Male	9	—	67±12	4.0±1.6	2.4±2.2	47±35	5
Female	10	—	67±15	4.1±1.9	3.0±2.2	30±33	6

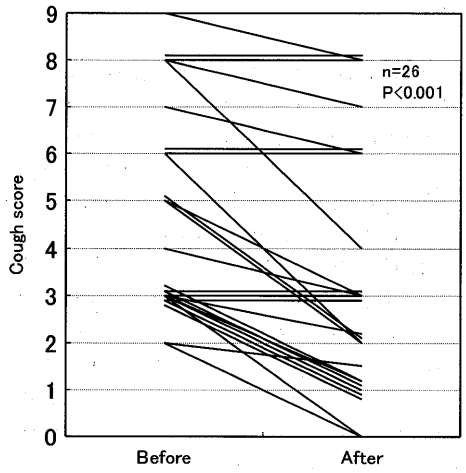

Fig. 2 Effectiveness of montelukast sodium (Total cases)

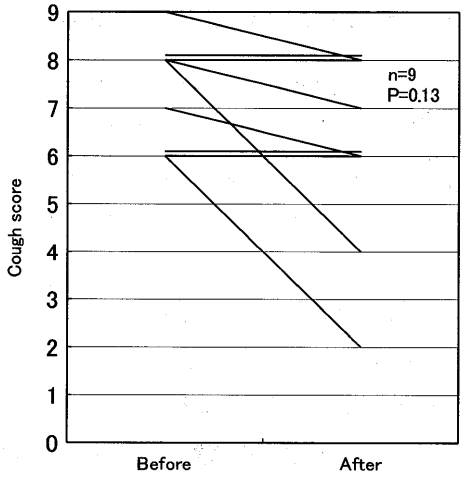

Fig. 3 Effectiveness of montelukast sodium (High score cases)

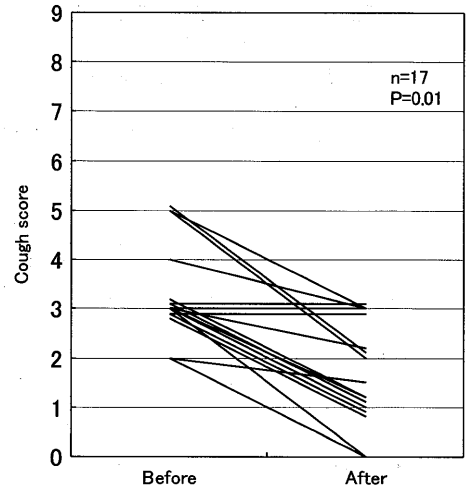

Fig. 4 Effectiveness of montelukast sodium (Low score cases)

observed between the non elderly and the elderly cases, nor between the male and female cases (P=0.33, P=0.20, respectively). Among all of the cases, MT improved the rate of CS by 37±33%, from 4.7±2.2 to 3.2±2.5 points after a 2-week course of therapy, as shown in Fig. 2 (P<0.001). Among high score cases, MT improved the rate of CS by 19±24%, from 7.1±1.3 to 5.8±2.2 points, as shown in Fig. 3 (P=0.13). Among low score cases, MT improved the rate of CS by 48±34%, from 3.1±0.9 to 1.6±1.0 points, as shown in Fig. 4 (P=0.01).

Discussion

The present study shows that: 1) MT is effective in patients with recurrent CVA, especially in low score cases; 2) the CS before MT administration is negatively correlated with i-CS, and therefore the CS is regarded as a clinical parameter of the therapeutic responsiveness and severity of CVA; 3) age and gender are not regarded as clinical parameters. The number of cases in the present study was limited, and age and gender are not considered to be clinical parameters. However, further examination should be performed. The elderly cases and the female cases were somewhat poorly responsive, though this poor responsiveness was not statistically significant. As possible causes of this lower responsiveness, we note that there were more cases of the non atopic type in the elderly compared to the non elderly in the present study, and a more sensitive cough reflex was reported in females than in males (Dicpinigaitis et al., 1998).

Eosinophilic inflammation and remodeling have been observed in CVA as well as bronchial asthma (Niimi et al., 2000). Approximately 30% of patients with CVA are thought to shift to having bronchial asthma. The general consensus on bronchial asthma is that early intervention with inhaled steroids should be used to prevent respiratory tract remodeling, but as for CVA, the optimal treatment course remains unclear. Though β_2-agonists immediately improve the cough symptoms of CVA, more than a few cases ultimately require concomitant regimens, including inhaled or oral corticosteroids (Niimi et al., 1998; McGarvey et al., 1999). However, therapeutic compliance is an important problem with inhaled steroid therapy in patients with not only bronchial asthma but also CVA. It is difficult for most patients with CVA

to continue undergoing that therapy when cough is the sole manifestation. Given that there is high compliance with a treatment with once daily MT, and that steroid therapy does not completely suppress leukotriene (LT) in the urine of asthmatics (Manso et al., 1992 ; O'Shaughnessy et al., 1993), the sole or concomitant administration of MT is very useful in patients with CVA. In elderly patients, the number of cases with various complications including hypertension, ischemic heart disease, glaucoma, prostate hypertrophy, et al., which should be carefully treated by bronchodilators, is greater, and some elderly patients also find it difficult to use the devices with which they inhale the steroids. Because MT is useful to the elderly as well as the non elderly, elderly cases are considered to be more actively indicated for MT therapy.

With respect to the pathophysiology of CVA, various chemical mediators concerned with CVA have been reported. Brightling and his colleagues have reported that histamine and prostaglandin D_2 originating from mast cells are elevated in induced sputum of patients with CVA, eosinophilic bronchitis (EB), and idiopathic chronic cough (ICC), but not in patients with bronchial asthma (Brightling et al., 2000 ; Birring et al., 2004). They have also reported that cysteinyl-LT that originates from eosinophils is elevated in induced sputum of patients with bronchial asthma (most elevated), CVA, and EB, but not in those with ICC. They have recently compared bronchial biopsy characteristics between bronchial asthma, EB, and healthy subjects (Brightling et al., 2002). The subjects with asthma were found to have AHR, whereas those with EB had normal airway responsiveness. Intriguingly, the degree of mucosal eosinophil infiltration and subepithelial fibrosis have been found to be similar between asthma and EB, possibly indicating that AHR could not be induced by eosinophilic inflammation or remodeling. The important difference between the groups was the presence of mast cell infiltration in the airway smooth muscle in asthma, which was absent in EB. This may suggest that AHR is closely linked to airway smooth muscle mast cells or its derived chemical mediators. In asthmatics, AHR has been thought to be a downstream phenomenon induced by chronic eosinophilic inflammation, but data showing that AHR is induced by interleukine-5 (Rizzo et al., 2002), phospholipase A2 (Takata et al., 1999), and tryptase (Sekizawa et al., 1989 ; Brightling et al., 2002) and others independently of eosinophilic inflammation have recently been accumulated.

Considering the above-mentioned reports and others, the following can be postulated for non asthmatic chronic cough : chronic airway eosinophilic inflammation spreads from the large to the small airway, or from the inner to the outer layer, and its inflammation induces various mediators such as histamine, neuropeptides including substance P (the most likely candidate of cough-inducing substances), bradykinin, calcitonin gene-related peptide, and lipid mediators including LT, prostaglandin, thromboxane, et al. These conclusions suggest the following : broader lesions exist in the large and small airways, and in the inner and outer layers in bronchial asthma ; though the degree of the lesion would be slight in CVA, the distribution would be similar to that in bronchial asthma (therefore, the more broadly the lesion spreads, the more prone the cases with CVA would be to shift into bronchial asthma in the future) ; if the lesion is limited to a comparatively large airway and the inner layer, its clinical phenotype would be EB, as described by Gibson et al. (1989), or atopic cough (AC), as described by Fujimura (1992). This hypothesis can explain the clinical epidemiology in which typical asthma onset has been recognized in nearly 30% of patients with CVA, but not in AC/EB. In direct discussion between the two researchers (Fujimura and Gibson, 2001), it appears that there is considerable overlap between EB and AC, which are recognized as the conditions that reveal normal airway responsiveness and airway cough hypersensitivity to inhaled capsaicin, and respond to corticosteroids with suppression of cough and of sputum eosinophilia.

Conclusions

Based on the MT responsiveness presented here, the drug appears to be involved in improving approximately 73% of CVA cases, regardless of age and gender. With respect to cause therapy, drug compliance, understanding inhaled therapy, and the complications prevalent in the elderly, elderly cases are considered to be more actively indicated for MT therapy. The present study recommends the concomitance of β_2-agonist or inhaled (or oral)

corticosteroid with MT in severe cases at the early stage of treatment.

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