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Original Paper

The leukotriene receptor antagonist montelukast sodium is effective in patients with recurrent bronchodilator-unresponsive chronic dry cough

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Abstract

There have been extremely a few reports regarding the effectiveness of leukotriene receptor antagonist (LTRA) in the treatment of patients with bronchodilator-unresponsive chronic dry cough (BU-CDC).

Methods : Research on 12 patients (4 males, 8 females, 9 with atopic factors ; age 41 ±18 yrs) with BU-CDC was carried out to investigate the effects of a 2-week course of the LTRA montelukast sodium (MT) at a dosage of 10 mg once daily. The patients studied had a cough that had persisted for over 4 weeks, which had already failed to be treated with a 2-week course of the β_2-adrenoreceptor agonist. Their response to MT was clinically judged using a cough score (CS).

Results : (1) Of the 12 cases studied, 4 cases (33%) showed a good response, 3 (25%) showed a moderate response, and 5 (42%) showed no response. In the total cases, the rate of effectiveness was 58%, and the improvement rate of CS (i-CS) was 28% ($P=0.03$). (2) The duration of the cough was negatively correlated with the i-CS ($r=-0.48$, $P=0.08$), but there was no correlation between the cough severity and the i-CS. (3) Sub-analysis showed that the longer the cough persisted, the poorer the responsiveness was ; the i-CS was, 15% in 6 cases with a cough persisting for over 8 weeks, and 40% in 6 cases with a cough persisting for less than 8 weeks ($P=0.10$). There were no significant differences between the high CS cases and low CS ones, or between the male cases and female ones.

Conclusions : MT is effective not only in the treatment of patients with bronchial asthma and cough variant asthma, but also in the treatment of patients with BU-CDC, mostly corresponding to eosinophilic tracheobronchitis with cough hypersensitivity (Fujimura et al) or eosinophilic bronchitis without asthma (Gibson et al).

Key words : Montelukast sodium, Leukotriene receptor antagonist, β_2-adrenoreceptor agonist, Atopic cough, Eosinophilic bronchitis without asthma

Introduction

Cough is a common clinical symptom not only in respiratory clinics but in general practice. The causes of chronic cough that persist for more than 4 weeks are diverse, and diagnosing these causes and prescribing therapy can be difficult. Although gastroesophageal reflux-associated cough, postnasal drip-induced cough, post-infectious cough and angiotensin-converting enzyme inhibitor-induced cough are among the known causes of chronic cough, most of the other causes of chronic cough, excluding the causes men-

tioned above, are thought to be due to non-asthmatic eosinophilic airway diseases such as cough variant asthma (CVA), atopic cough (AC) and eosinophilic bronchitis without asthma (EB), followed by eosinophilic airway inflammation (Irwin et al., 1990 ; Fujimura et al., 2001 ; Yamasaki et al., 2003).

CVA, which was described by Corrao et al. (1979), has been recognized as a variant form of bronchial asthma ; namely, the conditions that reveal normal spirometry but airway hyperresponsiveness when examined by methacholine. Bronchodilators are an effective therapy for CVA, and can be used for clinical diagnosis. However, AC, which was described by Fujimura et al. (1992), has recently been recognized as eosinophilic tracheobronchitis and airway cough hypersensitivity. Clinically, AC reveals normal spirometry, normal airway responsiveness, and airway cough hypersensitivity to inhaled capsaicin. In terms of therapy, AC can be successfully treated with H_1-antagonists and/or corticosteroids. In Western countries, EB, which was described by Gibson et al. (1989), has been recognized as a condition that reveals normal airway responsiveness and airway cough hypersensitivity to inhaled capsaicin, and that responds to corticosteroids, which suppress the cough and sputum eosinophilia. In direct discussion between these two researchers, it appears that there is considerable overlap between AC and EB (Fujimura and Gibson, 2001).

The leukotriene receptor antagonist (LTRA) has recently been positioned as an important drug in bronchial asthma, which is the typical condition of airway inflammation with eosinophilia. We previously reported on the efficacy of the LTRA montelukast sodium (MT) in the treatment of patients with CVA (Yamasaki 2003). There is very little evidence, however, and very few reports, on whether or not LTRA is effective in patients with bronchodilator-unresponsive chronic dry cough (BU-CDC) mostly corresponding to AC and/or EB.

To rectify this lack, therefore, we examined whether or not MT is effective in patients with BU-CDC.

Methods

Study Subjects

Twelve cases diagnosed as BU-CDC in the following study protocol were included (4 males, 8 females ; age 41±18 yrs). They were referred to our clinic of internal medicine between November, 2001 and May, 2004 after complaining of chronic cough. The patients granted their informed consent before being enrolled in this therapeutic protocol.

Methods

(1) Diagnosis of BU-CDC

The cases manifesting a dry cough that had persisted for over 4 weeks and was 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 who had taken 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. In addition, laboratory tests, including hematological tests with inflammatory reaction and total IgE in total cases, serum antibody for mycoplasma, chlamydia pneumoniae and pertussis, and a sputum culture and an induced sputum test were given, if deemed necessary. The non-organic recurrent cases were treated with the β_2-adrenoreceptor agonist (β_2-agonist); 11 cases were treated with tulobuterol tape at a dosage of 2mg a day for two weeks, and 1 case was treated with salmeterol xinafoste at a dosage of 100μg a day for two weeks. When the cough symptoms did not show any improvement, BU-CDC was diagnosed clinically. In the present study, we only selected the recurrent cases that were completely resistant to the β_2-agonist and that responded to inhaled corticosteroid (beclometasone dipropionate), 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 three 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 symptoms were graded as described below. The CS, ranging from 0 to 9 points, was then 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, frequent coughing, which was so severe that it was difficult to talk or telephone, and/or was so severe that sleep was continuously disturbed.

(3) Study Protocol of MT administration

The subjects diagnosed with BU-CDC were treated with 10 mg of MT once daily for 2 weeks. We classified cases in which the CS had improved over 50% as a good response (effective), cases without changes in the CS as no response (ineffective), and the rest as moderate response (slightly effective). If the CS reached O during treatment, MT was no longer administered. If the CS did not decrease to less than 50% of the baseline during the 2 weeks of MT administration, inhaled corticosteroid at a dosage of more than 600μg daily plus H_1-antagonists were added to the treatment regime. If the CS still did not change, the treatment regime of MT was altered to inhaled corticosteroid at a dosage of more than 600μg daily plus H_1-antagonists.

(4) Evaluation Items and Statistical Analysis

The efficacy of the drug was judged after a 2-week administration of MT using the CS. The improvement rate of the CS (i-CS) was calculated ; CS before MT(b-CS)−CS after MT (a-CS)/CS before MT×100 (%).

①The therapeutic efficacy was evaluated using the rates of the CS before and after the administration of MT in the total cases. ②The correlations were analyzed among age, duration of the cough (DC), and the b-CS, a-CS and i-CS. ③According to the results of the correlation coefficients, the cases were divided in reference to the following clinical parameters, and the therapeutic effectiveness was analyzed using i-CS : Ⓐhigh score cases (CS≧6 points) versus low score cases (CS≦5points), Ⓑthe cases with a chronic cough persisting for more than 8 weeks versus the cases with a chronic cough persisting for less than 8 weeks, and Ⓒmale cases versus female cases. Since each group drawn from the total cases was not completely condition-matched, the results obtained were interpreted as information to be used for reference.

Statistical analyses were carried out as follows. The correlations were analyzed by Pearson's correlation coefficient test. 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 cases of Ⓐ, Ⓑ, Ⓒ. A p value of less than 0.05 was considered statistically significant. A p value of less than 0.10 was considered to indicate statistical tendency.

Results

The summary is shown in Table 1. No cases worsened or showed adverse effects. There were 4 males and 8 females studied. Of these 12 cases, 9 cases (75%) showed atopic factor-related data, including allergic rhinitis, allergic dermatitis, increase of eosinophils in the peripheral blood, or increase of total IgE. In contents of the treatment, successful therapy was achieved in 5 cases by MT alone, and of 6 cases with chronic cough that had persisted for less than 8 weeks, successful therapy was achieved in 4 cases by MT alone. Four cases (33%) showed a good response, 3 cases (25%) showed a moderate response, and 5 cases (42%) showed no response (Fig. 1). The efficacy of the MT was found to be 58%. Among all of the cases, MT improved the rate of i-CS by 28±26%, from 4.7±1.6 to 3.4±1.9 points after two weeks of therapy (Fig. 2, P=0.03). There was a negative weak correlation between the b-CS and DC (r=−0.48, P=0.08). The b-CS was not correlated with the i-CS (r=

Table 1 Summary of cases with recurrent bronchodilator-unresponsive chronic dry cough

Case	male/female	age	Duration of cough (weeks)	CS (before)	CS (after)	i-CS (%)	atopic factor
Total cases	4/8	41±18	8.2±5.8	4.7±1.6	3.4±1.9	28±26	9/12
High score	1/5	42±20	6.7±3.3	6.0±0.9	4.5±2.1	26±29	4/6
Low score	3/3	40±19	9.7±7.6	3.3±0.5	2.3±0.8	29±27	5/6
Duration≧8W	2/4	45±25	12±6.2	4.8±1.7	4.3±2.3	15±27	6/6
Duration<8W	2/4	37±10	4.3±0.7	4.5±1.5	2.5±0.6	40±22	3/6
Male	—	45±16	10±9.5	4.0±2.0	2.3±1.0	40±30	4/4
Female	—	38±20	7.3±3.4	5.0±1.3	4.0±2.0	22±25	5/8

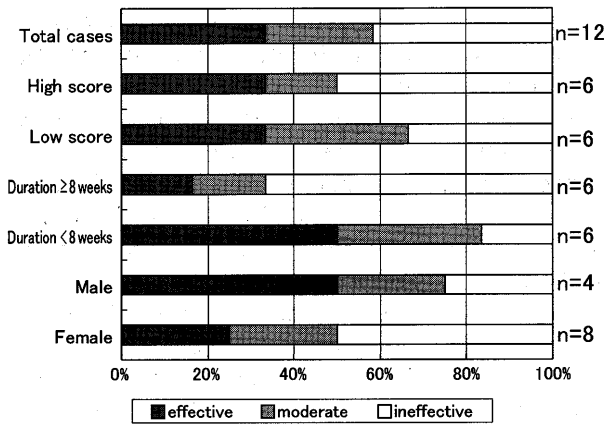

Fig. 1 Effectiveness of montelukast sodium in patients with bronchodilator- unresponsive chronic dry cough
Of the 12 cases studied, 4 cases showed a good response, 3 showed a moderate response, and 5 showed no response. The duration of the cough influenced the effectiveness of montelukast sodium. Montelukast sodium was more effective in the cases with chronic cough that had persisted for less than 8 weeks than in those that had persisted for more than 8 weeks

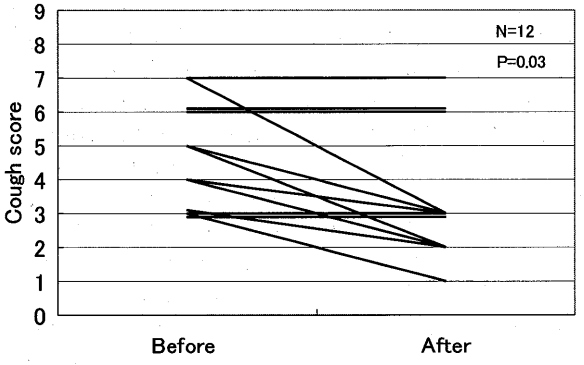

Fig. 2 Changes in the cough score after treatment of bronchodilator- unresponsive chronic dry cough using montelukast sodium (total cases)
Changes in the cough score after a 2-week course of therapy is shown. Cough score: 4.7±1.6→3.4±1.9; the improvement rate of the cough score: 28±26% (P=0.03)

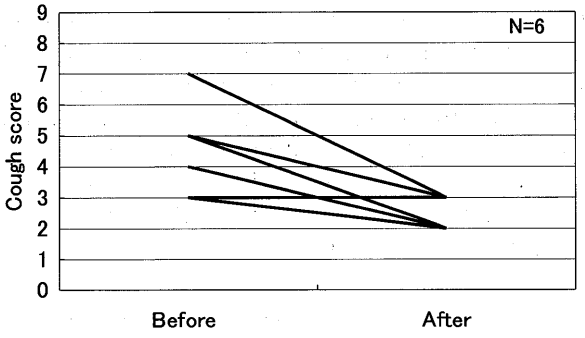

Fig. 3 Changes in the cough score after treatment of bronchodilator- unresponsive chronic dry cough using montelukast sodium (<8 weeks)
Of 6 cases, 3 cases showed a good response, 2 cases a moderate response, and 1 case showed no response. Cough score: 4.5±1.5→2.5±0.6; the improvement rate of the cough score: 40±22% (P=0.10)

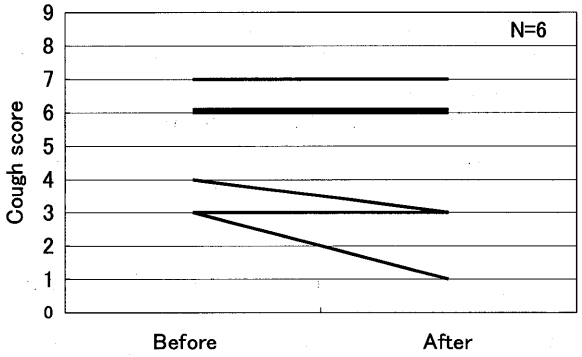

Fig. 4 Changes in the cough score after treatment of bronchodilator- unresponsive chronic dry cough using montelukast sodium (≧8 weeks)
Of 6 cases, 1 case showed a good response, 1 case showed a moderate response, and 4 cases showed no response. Cough score: 4.8±1.7→4.3±2.3; the improvement rate of the cough score: 15±27%

−0.11, P=0.50). The other parameters did not correlate with each other. There was a statistical tendency for the differences of therapeutic responsiveness both between the cases with chronic cough that had persisted for over 8 weeks, and those cases in which the cough had lasted less than 8 weeks (Table 1, Fig. 1, P=0.10). Significant differences in therapeutic responsiveness were not observed between the low score cases and high score ones, nor between the male and female cases, respectively. In the cases with a chronic cough that had persisted less than 8 weeks, there was more efficacy than in the cases in which the cough had persisted over 8 weeks (Fig. 1, Fig. 3, Fig. 4, P=0.01, the improvement of the CS: 4.8±1.7 to 4.3±2.3, i-CS 15±27% versus 4.5±1.5 to 2.5±0.6, 40±22%).

Discussion

Airway eosinophilic inflammation is now reported to occur not only in bronchial asthma, but also in other airway diseases, such as CVA, AC, and chronic cough. CVA is one

entity with airway hyperresponsiveness responding to bronchodilators, and AC or EB (the concept of which considerably overlaps, as was mentioned in the Introduction), is another entity with airway cough hypersensitivity and normal airway responsiveness resistant to bronchodilators. There is a third entity of idiopathic chronic cough (Birring et al., 2004), in which they have not clinically confirmed airway eosinophilic inflammation.

It is estimated that bronchial asthma and CVA are among the most important causes of chronic cough (Irwin et al., 1990 ; Brightling et al., 1999 ; Fujimura et al. 2001 ; Yamasaki et al., 2003). In Japan, the causes of chronic dry cough, except for post-infectious cough, gastroesophageal reflux-associated cough, and drug-induced cough are assumed to be CVA and AC, the rate of which amounts to more than 80% of patients with chronic dry cough. The ratio of CVA : AC is equal to 1 : 2 in their university hospital (Fujimura et al., 2001), and the ratio of CVA : AC-highly suspected cases is equal to 2 : 1 in our Internal Medicine clinic (Yamasaki et al., 2003). Then, as mentioned below, we discussed the pathophysiology of BU-CDC, in view of the conception that a large number of cases with BU-CDC correspond to AC/EB. However, we discussed the pathophysiology of bronchodilator-responsive chronic dry cough (BR-CDC), in view of the conception that a large number of BR-CDC correspond to CVA. Namely, we have discussed the pathophysiology of BU-CDC using up-to-date evidence and information on AC/EB. However, the pathophysiology of non-asthmatic eosinophilic airway inflammation has not yet been determined in detail.

LTRA for bronchial asthma is listed as one of the most important drugs in the guidelines of the GINA (Global Initiative for Asthma). Some authors have reported the efficacy of MT in patients with CVA (Dicpinigaitis et al., 2002 ; Yamasaki, 2003). With regards to AC/EB, there have been very few reports on the efficacy of therapy with LTRA.

The rate of effectiveness in our study was 58%, when including both the cases that showed a good or moderate response. Although the rate of effectiveness in patients with BU-CDC did not reach the rate of 66% (Yamasaki, 2003), or 88% (Dicpinigaitis et al., 2002) reported previously in patients with CVA, this result is worthy of attention. However, the BU-CDC cases responded differently to LTRA than the CVA cases did. The b-CS was not correlated with the i-CS in BU-CDC. Namely, the clinical cough severity had no affect on the improvement of the cough symptoms. A chronic cough is the only sign or symptom and the determinant of QOL in patients with BU-CDC, but the CS is not assumed to reflect the severity of BU-CDC. In a subanalysis, the rate of effectiveness differed between cases with chronic dry cough that had persisted for over 8 weeks, and those with a cough that had persisted for less than 8 weeks. In the cases with a chronic dry cough that had persisted for less than 8 weeks, the rate of effectiveness and the i-CS reached 83% and 40%, respectively.

The present study showed that MT was effective for BU-CDC. Some interesting facts can be drawn from the present clinical data : ① The pathophysiology of BU-CDC is associated with cysteinyl-leukotrienes (LT) based on eosinophilic airway inflammation. ②Since LTRA improves BU-CDC without airway hyperresponsiveness, LT may be associated airway cough hypersensitivity with direct and/or indirect manners. ③LT is assumed to be one of the most important substances in not only CVA, but also BU-CDC, and it is recognized that LTRA is effective in both patients with CVA and in those with BU-CDC mostly corresponding to AC/EB.

It is difficult to interpret the different responsive manners to LTRA in patients with CVA and BU-CDC, and it is also difficult to determine the pathophysiology from the viewpoint of chemical mediator profiles. In order to discuss this further, a series of articles reported by Brightling and Birring et al. are briefly discussed below. We will also add some additional remarks.

Induced sputum chemical mediator concentrations are demonstrated as follows : the rate of LT concentrations, bronchial asthma > CVA = EB > control ; the rate of histamine (His) and prostaglandin D_2 (PGD_2) concentrations, CVA = EB > bronchial asthma = control. To summarize the chemical mediator profiles and therapeutic responsiveness, the followings are presented ; bronchial asthma, LT ↑ ↑, His→, PGD_2→, the responsiveness to LTRA (+), responsiveness to the H_1-antagonist (−) ; CVA, LT ↑, His ↑, PGD_2 ↑, the responsiveness to LTRA (+), the responsiveness to the H_1-antagonist (−) ; EB/AC, LT ↑, His ↑, PGD_2 ↑, the responsiveness to LTRA (+), and the

responsiveness to the H_1-antagonist (+). The interpretation for why the concentrations of His and PGD_2 are not elevated in the sputum of patients with bronchial asthma, is that the inflammatory phase shifted from an acute to delayed phase. The therapeutic responsiveness for bronchial asthma with LTRA and the H_1-antagonist respectively can be expressed as it has been experienced by clinicians in daily general practice. The effectiveness of MT for EB/AC in the present study can be inferred based on the evidence obtained from chemical mediator profiles. Although the chemical mediator profile of the elevated LT, His, and PGD_2 concentrations is the same as in CVA and EB/AC, airway hyperresponsiveness is obtained in CVA, and airway cough hypersensitivity is obtained in EB/AC. Since the LT concentration did not become elevated in idiopathic chronic cough, meaning that eosinophilia was not clinically proven, the elevation of the LT concentration is thought to be associated with airway eosinophilic inflammation. In contrast, the chemical mediator profile of elevated His and PGD_2 in idiopathic chronic cough may suggest that this profile is not important for airway hyperresponsiveness, but is important for chronic cough without airway hyperresponsiveness.

The H_1-antagonist is effective in about 60% of patients with AC (Fujimura et al., 2001). Thus, we must ask why the H_1-antagonist is not effective in patients with CVA, considering its chemical mediator profiles. This question has not been completely answered by the information which is currently available. The mechanism of chronic cough in CVA is basically due to airway hyperresponsiveness, which has been determined by clinical examination by methacholine and good responsiveness to bronchodilators. Consequently, the H_1-antagonist seems to be effective in patients with CVA in terms of CVA's chemical mediator profile, but clinically, it has actually not been shown to be effective. Although CVA cases respond to bronchodilators, there have been more than a few cases with CVA which could not be effectively treated only with bronchodilators (Niimi et al., 1998 ; McGarvey et al., 1999 ; Fujimori et al., 2001). There is a possibility that a part of the mechanism of chronic cough in CVA is due to airway cough hypersensitivity defined in a broad sense not only by inhaled capsaicin, but also other substances such as substance P et al.) induced by the common mediator profile with EB/AC. However, since the mechanism of chronic cough in AC/EB is basically due to airway cough sensitivity which is directly and/or indirectly induced by His and/or PGD_2, the H_1-antagonist seems to be effective in patients with AC. Therefore we must ask why LTRA as well as the H_1-antagonist is effective in patients with BU-CDC mostly corresponding to AC/EB. There is no answer to this question at present, but the hypothesis is as follows. It is important to note that LT is associated with the mechanism of airway cough sensitivity in BU-CDC. Namely, there is a possibility that LT and His can interact with each other, and can trigger activity by the cough receptor. Another possibility is that a third substance, such as neuropeptides like substance P et al. as a well-established substance, stimulated by the simultaneous elevation of LT and His, should be postulated.

Why didn't patients with EB/AC obtain airway hyperresponsiveness regardless of the heightened LT? We answered this question by referring to a series of articles reported by Brightling and Birring et al.. We considered the differences in clinical phenotypes among eosinophilic airway diseases, in combination with inflammatory lesions and chemical mediator profiles. Namely, where is the main inflammation located, the inner layer or outer layer, or the small airway or large one? What kind of chemical mediators are involved, LT, prostaglandins, or neuropeptides? In bronchial asthma, airway inflammation is located diffusely in both the inner and outer layer, from the large to small airway. In CVA, although airway inflammation is located in both the inner and outer layer, and spreads from the large to small airway, similar to bronchial asthma, the degree and distribution of inflammation may be slight compared with bronchial asthma. It is estimated that the more broadly inflammation spreads in CVA, the more frequently it progresses to typical asthma. In terms of the chemical mediator profiles, LT plays an important role in bronchial asthma and CVA, but the similar inflammatory reaction in the inner layer of the large airway is found in both CVA and AC. Namely, in AC, airway inflammation is located in the inner layer of the large airway, and chronic cough is induced directly and/or indirectly in combination with LT, His, and neuropeptides followed by its neurogenic inflam-

mation (Barnes, 1986) because these substances stimulate each other (Bloomquist et al., 1987 ; Widdicombe, 1996 ; Forsythe et al., 2000 ; Andoh et al., 2001).

Recently, Brightling et al. (2002) indicated that airway hyperresponsiveness is linked to airway smooth muscle mast cell infiltration, which is consistent with the well established effects of mast cell mediators on airway smooth muscle contraction. Nagai et al. (1996) reported that airway hyperresponsiveness was not observed in mast-cell-deficient mice, despite no differences in the Interleukin-5 level and the number of eosinophils in the bronchoalveolar lavage fluid between mast-cell-deficient mice and control mice. It is inferred that the reason why EB/AC does not obtain airway hyperresponsiveness is due to mast cell infiltration and its reaction in airway smooth muscle.

Although b-CS correlated with cough severity in the treatment of CVA (Yamasaki, 2003), b-CS did not correlate with the therapeutic responsiveness of LTRA in BU-CDC. The severity of cough symptoms was not a predictor for the success of therapy, in contrast with CVA. This result is shown as follows: the cough symptom in CVA is mainly due to airway hyperresponsiveness and partially due to airway cough hypersensitivity, and the cough symptom in BU-CDC is mainly due to airway cough hypersensitivity and partially to airway hyperresponsiveness. Therefore, the way in which cough receptor hypersensitivity develops may be different from the way in which airway hyperresponsiveness develops, in view of the formation of cough symptoms associated with LT. This will be the subject of a future in-depth study. The subjects studied here were patients with cough symptoms that had persisted for over 4 weeks. The longer the cough persisted, the poorer the therapeutic responsiveness was, and this result suggests the possibility that chronic stimulation persists in nerve endings, such as the Aδ-fiber and C-fiber, and that, therefore, sensitization of the cough receptor occurs when a cough persists. It is postulated that LT is linked more closely with cough hypersensitivity in the early stage of cough symptoms than in the delayed stage. In any case, it is recommended that LTRA be used to treat chronic cough that is still in the early stages in patients with BU-CDC mostly corresponding to AC/EB.

Conclusions

Evidence of LTRA in the treatment of patients with CVA has been accumulating, but there has been little evidence of LTRA in the treatment of patients with BU-CDC. The present research suggested that MT is effective not only in the treatment of patients with bronchial asthma and cough variant asthma, but also in the treatment of patients with BU-CDC, mostly corresponding to eosinophilic tracheobronchitis with cough hypersensitivity (Fujimura et al) or eosinophilic bronchitis without asthma (Gibson et al).

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