

Case Report

Effect of suplatast tosilate on cough variant asthma

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ABSTRACT

A 40-year-old female patient with chronic persistent cough was diagnosed with cough variant asthma (CVA). To investigate the effect of suplatast tosilate (suplatast, 300 mg/day, three times a day), cough scores, medication scores, pulmonary function, capsaicin cough threshold, bronchial hyperresponsiveness (BHR) to methacholine and eosinophilic cationic protein (ECP) concentration in hypertonic saline-induced sputum were evaluated before and after a 6-week treatment with suplatast. Treatment with suplatast resulted in a marked decrease in persistent cough and in the percentage of eosinophils and ECP concentration in induced sputum. It also resulted in a marked improvement in capsaicin cough threshold and a slight improvement in BHR. These results suggest that suplatast tosilate may be useful for treating patients with CVA.

Key words: asthma, capsaicin, cough threshold, cough variant asthma, eosinophilic cationic protein, suplatast, T helper 2 cell-derived cytokine inhibitor.

INTRODUCTION

Cough is one of the main symptoms of respiratory disease. It has been reported that chronic persistent cough is the only manifested clinical symptom in patients

with cough variant asthma (CVA).^{1,2} Episodic wheezing is one of the criteria of bronchial asthma, but there is no history of wheezing in CVA patients.^{1,2} Although the precise mechanism responsible for the induction of cough in CVA patients is not clear, bronchodilators, such as β_2 -adrenoreceptor agonist and theophylline, are effective agents in relieving cough.^{3,4}

Suplatast tosilate (suplatast) has been shown to inhibit the production of Th2 cell-derived cytokines; interleukin (IL)-4 and IL-5.^{5–7} Recently, suplatast has been reported to be effective in mild asthma,⁸ but the effectiveness of suplatast in the treatment of CVA has not been clearly demonstrated.

In the present paper, we report on a case in which suplatast improved persistent cough score and the capsaicin cough threshold and also induced a reduction in the percentage of eosinophils and eosinophilic cationic protein (ECP) concentration in hypertonic saline-induced (induced) sputum, suggesting improvement in eosinophilic inflammation.

CLINICAL SUMMARY

A 40-year-old female patient visited Akita University Hospital on 12 May 1998, because of a dry cough that had persisted for 6 months. Although she had been treated with antibiotics and antitussive drugs by a general physician since January 1998, her cough had not improved. She had no history of asthma. Her cough usually began at night and often disturbed her sleep. The patient exhibited no wheezing, sputum, nasal discharge, fever or other symptoms, including gastroesophageal symptoms. The patient was 157 cm tall and weighed 43 kg. Her blood pressure was 128/64 mmHg, with no difference between arms. Her pulse was regular

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(96 b.p.m.). No heart murmur was heard and no rales were heard over either lung field.

As shown in Table 1, the patient's eosinophil differential was slightly elevated and her IgE level was within the normal range. The radioallergosorbent test (RAST) scores for house dust 1 (HD1), house dust mite (Der f), Japanese cedar and dog skin were positive (2 + to 3 +; Table 1). No abnormalities were detected by chest X-ray film or electrocardiogram. Pulmonary function tests showed no appreciable occlusion, with forced vital capacity (FVC) of 2.92 L, forced expiratory volume in 1 s (FEV₁) of 2.43 L,

FEV₁ as a percent of FVC (FEV_{1%}) of 83.2% and peak expiratory flow rate (PEF) of 4.43 L/sec (Table 2). There were no significant changes in PEF values between the morning and at night according to the asthma diary.

Bronchial response to inhaled methacholine (MCh) was assessed with an Astograph (TCK-6100H; Chest, Tokyo, Japan) for measurement of bronchial hyper-responsiveness (BHR). This device uses the forced oscillation method to measure respiratory resistance and its reciprocal conductance during tidal breathing.⁹ Airway sensitivity to MCh was expressed as the geometric mean of the lowest concentration of MCh associated with the start of a consistent decrease in conductance (Dmin, in mg/mL (unit) of MCh inhalation). Airway reactivity to MCh was expressed as the decrease rate of respiratory conductance (SGrs, in L/s per cmH₂O). Cough threshold was evaluated using capsaicin according to the method of Midgren *et al.*^{10,11} Briefly, capsaicin (Sigma Chemical Co., St Louis, MO, USA) was dissolved in ethanol and diluted with 0.9% NaCl to 0.016, 0.08, 0.4, 2, 10, 50 and 250 µmol/L. Capsaicin was inhaled during tidal breathing from a nebulizer (Nissho, Tokyo, Japan, output 0.5 mL/min, mean mass diameter 5 µm). Concentrations of capsaicin were increased until the patient coughed more than 5 times. The final concentration was taken as the cough threshold for capsaicin (Ccap: µmol/L).¹⁰

The patient evaluated her coughing four times a day, every 6 h, and recorded the cough points in the diary. The evaluations were 'quite often' (21 times or more), 4 points; 'often' (11–20 times), 3 points; 'relatively often' (6–10 times), 2 points; 'not often' (5 times or fewer), 1 point; and 'none', 0 points. The total cough points in a day became the cough scores. Inhalation of

Table 1 Laboratory findings on first visit

Hematology	
ESR (mm/h)	11
RBC (/mm ³)	412 × 10 ⁴
Hb (g/dL)	13.7
WBC (/mm ³)	7800
N	32%
Eos.	12%
Baso.	0%
Mono.	7%
Lymph.	49%
Plt (/mm ³)	27.7 × 10 ⁴
Biochemistry	
TP (g/dL)	8.2
Alb. (g/dL)	4.7
GOT (U/L)	28
GPT (U/L)	28
LDH (U/L)	168
ALP (U/L)	62
T. Chol. (mg/dL)	161
BUN (mg/dL)	10
Cr (mg/dL)	0.7
Na (mEq/L)	140
K (mEq/L)	3.9
Cl (mEq/L)	101
Serology and immunology	
CRP (mg/dL)	0.0
IgE (IU/mL)	172.1
RAST	
HD1	3+
Der f	3+
Jpn. cedar	3+
Dog skin	2+
Sputum eos.	35%

ESR, erythrocyte sedimentation rate; RBC, red blood cells; Hb, hemoglobin; WBC, white blood cells; N, neutrophils; Eos., eosinophils; Baso., basophils; Mono., monocytes; Lymph., lymphocytes; Plt, platelets; TP, total protein; Alb., albumin; GOT, glutamate oxaloacetate transaminase; GPT, glutamate pyruvate transaminase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; T. Chol., total cholesterol; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; RAST, radioallergosorbent test; HD, house dust.

Table 2 Time course in pulmonary function test

	12 May 1998	28 July 1998
FVC (L)	2.92	3.07
FEV ₁ (L)	2.43	2.49
FEV _{1%}	83.2	81.1
PEF (L/s)	4.43	4.67
Ccap (µmol/L)	2.0	50.0
Dmin (U)	3.8	6.2
SGrs (L/s per cmH ₂ O)	0.08	0.07

FVC, forced vital capacity; FEV₁, forced expiratory volume in 1 s; FEV_{1%}, FEV₁ as a percentage of FVC (FEV₁/FVC); PEF, peak expiratory flow rate; Ccap, capsaicin cough threshold; Dmin, geometric mean of the lowest concentration of methacholine associated with the start of a consistent decrease in conductance (in mg/mL of inhalation); SGrs, decreased rate of respiratory conductance.

the β_2 stimulant procaterol was also evaluated according to the standard set by the Japanese Society of Allergology, by counting each inhalation as 0.5 points.¹² Total inhalation points in a day were evaluated as medication scores. Astograph results showed a slight increase in BHR, with a Dmin of 3.8 units and SGRs of 0.08 L/s per cmH₂O. In contrast, the capsaicin cough threshold was markedly increased, as indicated by a Ccap of 2.0 $\mu\text{mol/L}$.

Airway inflammation was determined by counting the percentage of eosinophils and ECP concentrations¹³ in induced sputum. We used a radioimmunoassay¹⁴ with a Pharmacia Kit (Pharmacia Co., Tokyo, Japan) to measure the ECP concentration, which was elevated (4530 $\mu\text{g/L}$) in induced sputum. The percentage of eosinophils in induced sputum was 35%. We did not evaluate the concentrations of IL-4 and IL-5 in the sputum.

The patient was treated with suplatast (300 mg/day three times a day) beginning on 26 May, when testing was completed. Her persistent cough improved clinically beginning on treatment day 5. Treatment with suplatast also resulted in significant improvement in the cough scores, based on patient diary entries, and medication scores, as determined by the frequency of β_2 stimulant inhalation (Figs 1,2). Although there was no marked difference between the pulmonary function test results before and after 6 weeks of treatment with suplatast, Dmin improved slightly from 3.8 to 6.2 units and Ccap improved markedly from 2.0 to 50.0 $\mu\text{mol/L}$ (Table 2). The IgE level was 168.2 IU/mL after the 6-week suplatast treatment. No eosinophils were detected in induced sputum after the 6-week treatment and the sputum ECP concentrations also fell markedly from 4530 to 210 $\mu\text{g/L}$. The treatment with suplatast was continued and the patient has been free from persistent cough.

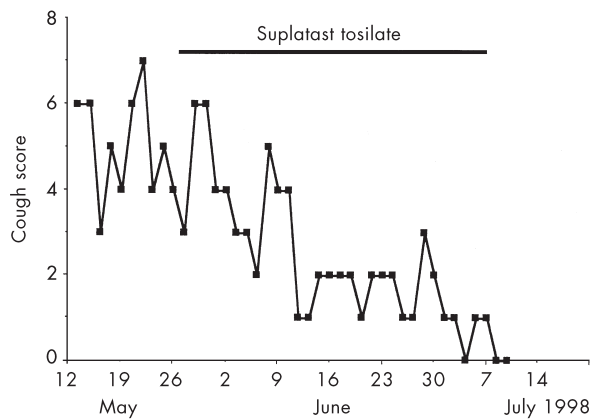


Fig. 1 Change in cough scores.

DISCUSSION

Treatment with suplatast resulted in the reduction of persistent cough, improvement in cough and medication scores, slight improvement in BHR, and marked improvement in the capsaicin cough threshold in a patient with CVA.

Cough is one of the main symptoms of respiratory disease. It is also not unusual for bronchial asthma patients to experience coughing alone as their chief complaint. An extreme example of this is CVA, the pathophysiology of which has been the focus of considerable interest.¹⁻⁴ Cough in CVA is elicited on the basis of the cough receptor sensitivity and bronchoconstriction.^{15,16} Anatomic and physiologic research has shown that the cough receptors that mark the starting point of the cough reflex pathway comprise rapidly adapting stretch receptors (RASR), located mainly in the central airways, and bronchial or pulmonary c-fibers, found in the peripheral airways.¹⁷ Substance P is regarded as one of the most influential neurotransmitters in these receptors.^{18,19}

Recently, suplatast has been shown to have immunoregulatory effects.⁵⁻⁷ Briefly, suplatast inhibits IgE production and degranulation of basophils or mast cells induced by IgE and suppresses production of IL-4 and IL-5 by T helper 2 (Th2) cells.^{5,6} Suplatast specifically inhibits production of IgE antibodies, but not IgG and IgM, in mice and also inhibits eosinophil infiltration in the same *in vivo* mouse model by suppressing Th2 cells.⁹ Treatment of patients with mild asthma has confirmed that suplatast significantly reduces eosinophil infiltration in the sputum and bronchial epithelium.⁸ Tsubura *et al.* have reported moderate improvement in 52.9% of adult bronchial asthma patients 5-6 weeks after treatment with suplatast at a dose of 300 mg/day.²⁰

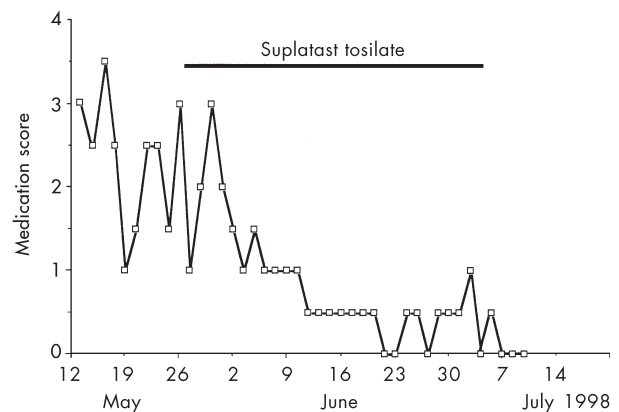


Fig. 2 Change in medication scores.

Our patient was diagnosed with CVA because of the absence of appreciable airway obstruction, although she had slightly increased BHR and elevated eosinophil percentage and ECP concentration in induced sputum. Treatment with suplatast, a Th2 cell-derived cytokine inhibitor, markedly reduced the patient's persistent cough and also resulted in significant improvement in cough and medication scores. The sputum eosinophil count also fell significantly and there was a marked reduction in ECP concentration, suggesting an improvement in eosinophilic inflammation. The Dmin, an objective indicator of BHR, improved slightly from 3.8 units before treatment to 6.2 units after treatment and Ccap, an objective indicator of cough hypersensitivity, improved significantly from 2.0 $\mu\text{mol/L}$ to 50.0 $\mu\text{mol/L}$, suggesting that suplatast may be useful for the treatment of cough in patients with CVA. Suplatast appeared to reduce eosinophilic airway inflammation by suppressing the production of Th2 cell-derived inflammatory cytokines, such as IL-4 and IL-5, as suggested by the marked reduction in sputum eosinophil count and ECP concentration observed in our patient. However, inflammatory cytokines such as IL-4 and IL-5 in the sputum need to be evaluated to verify this hypothesis. In addition, suplatast produced more a marked reduction of cough hypersensitivity than BHR, suggesting that suplatast may have inhibited eosinophilic inflammation of the cough RASR itself. Further basic research is needed to explain the precise mechanism by which suplatast inhibits cough in patients with CVA. The usefulness and mechanism of action of suplatast in relation to cough in CVA should be explored in more detail by conducting a case-controlled study of the drug in a large sample size at multiple institutions to investigate cough hypersensitivity and BHR and further evaluate sputum inflammatory cytokines.

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