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PHARMACOTHERAPY

Effects of regular treatment with combination of salmeterol/fluticasone propionate and salmeterol alone in cough variant asthmaEtsuko Tagaya, MD¹, Mitsuko Kondo, MD¹, Saori Kirishi, MD¹, Michi Kawagoe, MD², Noriyuki Kubota, MD³, and Jun Tamaoki, MD¹¹First Department of Medicine, Tokyo Women's Medical University, Tokyo, Japan, ²Department of Medicine, Hamacho Center-Building Clinic, Tokyo, Japan, and ³Joto Social Insurance Hospital, Tokyo, Japan**Abstract**

Objective: Cough variant asthma (CVA) is an important cause of chronic cough, and pathophysiological features of the disease appear to be similar to typical asthma. Because CVA is recognized as a precursor of asthma, early intervention with long-term anti-inflammatory agents may be recommended. However, the role of combination therapy with inhaled corticosteroid and β_2 -agonist in the treatment of CVA has not been elucidated. To evaluate the effectiveness of the combination therapy, we investigated the clinical impact of regular treatment with salmeterol/fluticasone propionate combination (SFC) and inhaled salmeterol (SAL) alone in patients with CVA. **Methods:** The study was a randomized, controlled, parallel-group multi-center trial. Forty-three CVA patients were assigned to SFC (50/100 μ g once daily) or SAL (50 μ g twice daily) for 12 weeks. Then, these medications were stopped for the next 24 weeks. Main outcome measures were cough symptoms, pulmonary function and airway inflammation. **Results:** Treatment with each of SFC and SAL significantly decreased cough scores and increased FEV₁ and PEF, where the efficacy was more pronounced with SFC than SAL. SFC also decreased sputum eosinophil counts and eosinophil cationic protein contents, whereas SAL had no effect. After discontinuation of the treatment, cough scores increased, pulmonary function and eosinophilic airway inflammation were aggravated and returned to the baseline levels. **Conclusions:** Maintenance therapy with SFC provides further improvements in cough symptoms, pulmonary function and airway inflammation, and discontinuation of the therapy causes worsening of the disease, indicating that stopping or interrupting anti-inflammatory therapy may not be advisable in patients with CVA.

Keywords

Airway inflammation, cough variant asthma, ICS/LABA, LABA, relapse rate

History

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Introduction

Cough variant asthma (CVA) is a major cause of chronic persistent cough and is considered a precursor of classic asthma or a preasthmatic state, because one-third of the patients who initially present with CVA eventually manifest typical symptoms of asthma, such as wheezing and dyspnea [1,2]. It has been reported that bronchodilators including β_2 -adrenergic agonist and theophylline are effective in relieving cough [3,4]. On the other hand, eosinophilic-associated cough, such as CVA is usually controlled by inhaled corticosteroids, implying a role for inflammatory factors [5] and recent international guidelines recommend that a combination of long acting β_2 -adrenergic agonist (LABA) and corticosteroid exerts potent anti-inflammatory effects and bronchodilation, and thus be used for the treatment of moderate-to-severe asthma [6]. However, such a combination therapy has not been recommended for maintenance treatment of mild asthma and CVA. We therefore studied the effect of

regular treatment with salmeterol/fluticasone propionate combination (SFC) and compared the efficacy with that of the bronchodilator salmeterol (SAL) alone in patients with CVA. To do so, we measured cough symptom scores, pulmonary function and markers of eosinophilic airway inflammation. In addition, it is unknown whether maintenance treatment of CVA can be discontinued after cough symptoms become stable. To elucidate this, we also examined the influence of discontinuation of the treatment.

Materials and methods**Patients**

Three centers participated. We recruited 47 subjects with newly diagnosed CVA aged 21 years and over, whose cough had been continuing at least for 8 weeks before the study. The cough was usually dry or productive with a scant amount of clear sputum. According to the Japanese cough guideline [7] and our consensus, CVA was diagnosed when the patient met the following criteria: (1) no history of wheezing or dyspnea; (2) no wheeze or prolonged expiratory phase detected on physical examination; (3) forced expiratory volume in 1 s

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(FEV₁) and forced vital capacity higher than the normal lower limits (80% predicted, each); (4) airway hyperresponsiveness to inhaled methacholine, which was defined as a PC₂₀ value (a concentration of methacholine required to produce a 20% decrease in FEV₁ from baseline) of <8 mg/ml; (5) relief of cough with a short-acting β_2 -agonist; and (6) no abnormal chest radiographic findings that could be responsible for the cough. Patients with other causes of chronic cough, such as chronic sinusitis, allergic rhinitis, gastroesophageal reflux disease and drug-induced cough, were excluded based on the history and physical examination, blood tests, chest roentgenogram and paranasal CT scan. Subjects were not included if they had been treated with inhaled or systemic corticosteroids, long acting β_2 -adrenergic agonists, anticholinergic agents or other controller medications for asthma within the previous 4 weeks. Written informed consent was obtained from each patient, and the study was approved by the Tokyo Women's Medical University Review Board and the local ethics committees.

Study design

The study was performed as a randomized, controlled, parallel-group, multi-center trial. After a 4-week run-in (baseline) period, all patients received either SFC (salmeterol/fluticasone propionate, 50/100 μ g once daily, via Discus (GlaxoSmithkline, Tokyo, Japan) or SAL (salmeterol, 50 μ g twice daily, via Discus; GlaxoSmithkline) for 12 weeks (treatment phase). Then, these medications were stopped during the next 24 weeks (follow-up phase).

Measurements

All patients visited an outpatient clinic every 2 weeks during the trial. On the first visit, demographic details were recorded. Each patient kept a daily record of all medications taken throughout the study. Symptoms of cough, morning and evening peak expiratory flow (PEF, best of three attempts before taking medication), were recorded daily. A 4-point scale was used to assess the severity of cough, with a score of 0 indicating the absence of symptom; a score of 1, mild cough; a score 2, moderate cough; and a score of 3, severe cough. Also, to assess the frequency of cough, a 5-point scale was used with a score of 0 indicating "none"; a score of 1, "not often" (5 times a day or fewer); a score of 2, "medium" (6–10 times); a score 3, "often" (11–20 times); and a score of 4, "very often" (>21 times) [8].

Patients were asked to record these scales every day, and at each visit, the physician calculated daily cough symptom scores as determined by multiplying the cough severity point by the cough frequency point. Therefore, the maximal daily score was 12, and e.g. if the patient produced moderate cough eight times a day, the daily score was 4.

At the end of the run-in period and at weeks 4, 8, 12 (treatment phase) and 16, 20, 24, 28, 32, 36 (follow-up phase) of the study period, FEV₁ was measured by CHESTAC 8800 system (Chest Co., Tokyo, Japan) at the clinic. We assessed atopy with serum-specific IgE antibodies against the following common aeroallergens: house dust mites; cat and dog dander; grass, tree, and weed pollens; molds; and feathers (RAST, SRL Laboratories Inc., Tokyo, Japan), and defined

atopy as one or more positive tests. To assess eosinophilic airway inflammation, eosinophil counts were measured in the peripheral blood and the sputum induced by hypertonic saline [9]. Concentrations of eosinophil cationic protein (ECP) in the serum and the sputum supernatant were measured by a radioimmunoassay using ECP radioimmunoassay kit (Pharmacia Diagnostic, Uppsala, Sweden) at the end of the run-in period and at weeks 4, 12 (treatment phase) and 24, 36 (follow-up phase) of the study period. In addition, at the baseline period and at weeks 12 and 36, mucin concentrations in the sputum supernatants were measured with the double-sandwich enzyme-linked immunoassay (ELISA) using 17Q2 antibody according to the method of Ordoñez [10].

To elucidate the impact of discontinuation of the treatment, we assessed relapse rate after stopping medication. The definition of relapse was as follows, occasional visits due to cough, oral/intravenous corticosteroid treatment, cough score increase by more than 30% compared with the previous week, or the more than 10 times in consecutive two days' use of supplemental β_2 -agonist.

Statistical analysis

Compliance with study medication was measured by calculating the percentage of scheduled doses recorded in the diaries. The values of PEF recorded in the diaries were reduced to weekly averages, and the averages for the last 1 week of baseline period were used as reference values. Symptom scores were reduced to monthly averages, which were compared with averages for the 4-week baseline period. Values for FEV₁, sputum cell counts, and sputum ECP and mucin concentrations were compared with those measured at the end of baseline period. All values were analyzed with respect to changes from the baseline value. Analyses within and between groups were performed by *t* test, and values of *p* < 0.05 were considered statistically significant.

Results

Of the 47 patients enrolled in the study, 4 patients were withdrawn during the 4-week run-in period because of missed clinic visits or incomplete PEF measurement, and remaining 43 patients were randomized to receive either SFC (*n* = 21) or SAL (*n* = 22). During the 12-week treatment phase, three patients were withdrawn from the two treatment groups because of missed clinic visits. During the next follow-up phase, two patients were withdrawn from the SFC group, one because of missed clinic visits and the other one because of discontinuation of PEF measurement, and three patients from the SAL group, one because of esophageal cancer (Figure 1). Thus, 35 patients completed the study and provided verifiable data (18 patients in the SFC group and 17 patients in the SAL group). Compliance during the treatment phase was not significantly different between the SCF and SAL groups (86 ± 3% versus 88 ± 3%). No clinically significant changes from baseline in physical examinations or laboratory evaluations were observed in either treatment group, and none of the patients dropped out because of adverse side effects.

Baseline patient characteristics are shown in Table 1. Although serum IgE levels were higher in the SFC group than those of SAL group, there were no significant differences

Figure 1. Study design. During the run-in period, 4 of 47 patients were excluded, and the remaining 43 patients were randomly assigned to receive either SFC (21 patients) or SAL (22 patients). During the 12-week treatment phase, three patients were withdrawn from the two treatment groups because of missed clinic visits. During the next follow-up phase, two patients were withdrawn from the SFC group, one because of missed clinic visits and the other one because of discontinuation of PEF measurement, and three patients from the SAL group, one because of esophageal cancer.

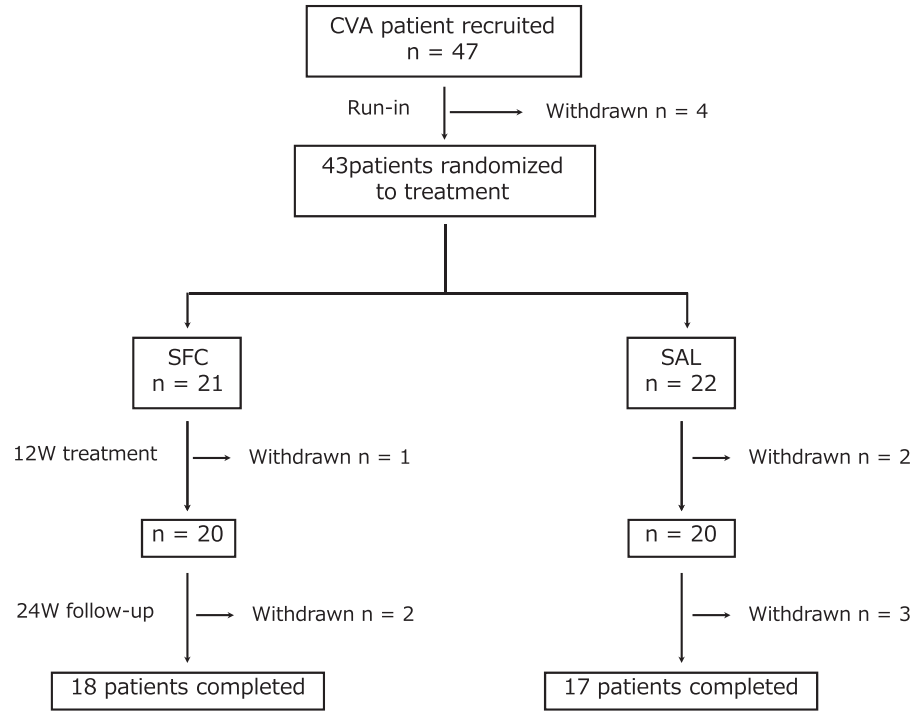


Table 1. Baseline patient characteristics.

	SFC (n = 18)	SAL (n = 17)
Men/women, n/n	8/10	8/9
Age, years	44 ± 3	39 ± 4
Atopy, n	16	16
Smoker/ex-smoker/nonsmoker, n	1/5/12	1/3/13
Duration of cough, weeks	27 ± 8	24 ± 6
Daytime cough symptom scores	6.3 ± 0.7	6.2 ± 0.6
Serum IgE, IU/mL	352 ± 31*	216 ± 27
FEV ₁ , % of predicted	84.6 ± 3.0	86.3 ± 2.1
PEF		
Morning PEF, L/min	448 ± 38	473 ± 45
Evening PEF, L/min	485 ± 29	507 ± 38
Morning PEF, % of predicted	86.1 ± 4.6	90.7 ± 5.0

SFC salmeterol/fluticasone propionate combination; SAL long-acting β_2 -agonist (salmeterol); FEV₁ forced expiratory volume in 1 s; PEF peak expiratory flow.

All means are expressed mean ± SEM.

* $p < 0.05$, significantly different from the values for SAL group.

between the two treatment groups at baseline in terms of age, sex, smoking status, atopy and duration of cough symptoms.

Asthma symptoms

As shown in Figure 2, during the 12-week treatment, daytime cough scores decreased from 6.4 ± 0.6 to 1.1 ± 0.3 ($p < 0.001$) in the SFC group and from 6.3 ± 0.5 to 3.4 ± 0.4 ($p < 0.01$) in the SAL group. With respect to the change of symptom scores from the baseline values, a significantly greater decrease was noted in the SFC group compared with the SAL group at both daytime and nighttime. During the following follow-up phase, cough symptom scores remained decreased in both treatment groups until week 16. At week 24–28, symptom scores tended

to increase in both groups and returned to baseline levels at week 36 in the SAL group.

Pulmonary function

Mean morning PEF and mean evening PEF increased in both groups during the 12-week treatment phase. During the following follow-up phase, morning PEF and evening PEF in both groups decreased and returned to the baseline levels at week 36 (Figure 3).

During the treatment phase of study period, FEV₁ in the SAL group increased by 0.18 ± 0.031 from the baseline value at week 4, while FEV₁ in the SFC group increased by 0.12 ± 0.021 , and there was a significant difference between the two treatment groups with respect to the change from baseline ($p < 0.05$; Figure 4). At week 12, the increase in FEV₁ from baseline was 0.22 ± 0.041 in the SAL group and 0.26 ± 0.051 in the SFC group, where the magnitude of change was not significantly different between the two groups. After discontinuation of the treatment, FEV₁ in both SAL group and SFC group gradually decreased and returned to baseline levels at week 36.

Markers of airway inflammation

During the 12-week treatment phase, eosinophil counts in the SFC group significantly decreased from $6.4 \pm 1.9\%$ to $4.0 \pm 1.6\%$ in the blood ($p < 0.01$) and from $17.8 \pm 6.7\%$ to $4.8 \pm 1.9\%$ in the sputum ($p < 0.01$). In contrast, significant decreases from the baseline in eosinophil counts were not observed in the SAL group (Figure 5). As with eosinophil counts, the concentrations of ECP in the serum and those in the sputum supernatants significantly decreased at week 12 in the SFC group, but they remained unchanged in the SAL group. After stopping medication, the values in the SFC group gradually increased and returned to the baseline levels at week 36 (Figure 6).

Figure 2. Changes in cough symptom scores in patients with CVA. After a 4-week run-in period, patients received SFC or SAL for 12 weeks, and these medications were stopped for the next 24 weeks. Values are mean $\pm$ SE; $n = 18$ –22 for each point.

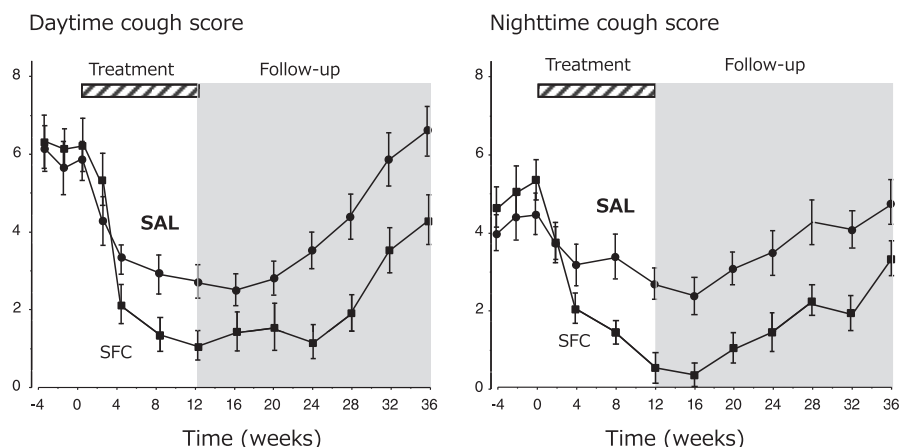


Figure 3. Changes in morning and evening PEF in patients with CVA during run-in period and the following treatment and follow-up phases. Values are mean $\pm$ SE; $n = 17$ –22 for each point.

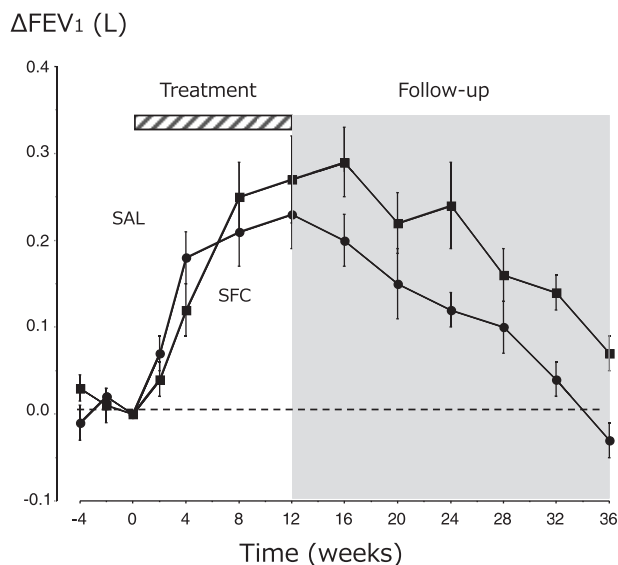
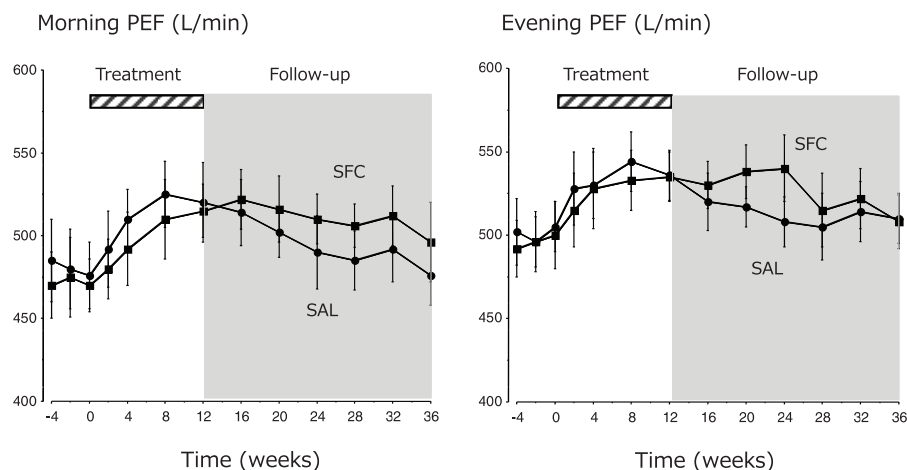


Figure 4. Changes in FEV₁ in patients with CVA during run-in period and the following treatment and follow-up phases. Values are mean $\pm$ SEM; $n = 16$ –22 for each point.

Sputum mucin contents

At the end of run-in period, there were no significant differences between the SFC group and the SAL group in term of the sputum mucin contents. After 12-week treatment

period, the sputum mucin contents decreased from 27.7 ± 4.8 to 11.6 ± 7.4 $\mu\text{g/ml}$ in the SFC group ($p < 0.05$), whereas these values did not significantly change in the SAL group (Figure 7). During the follow-up phase, mucin contents in the SFC group increased to 31.0 ± 6.2 $\mu\text{g/ml}$ at week 36, which was not significantly different from the baseline levels.

Relapse rate of symptoms

To assess relapse of CVA, we performed Kaplan–Meier analysis representing the cumulative percentages of patients whose symptoms worsened after discontinuation the therapy. As shown in Figure 8, there was no relapse during the treatment phase in both groups. However, during the 24-week follow-up phase, the number of patients with relapses increased in both groups, and the cumulative incidence rates were 100% in the SAL group and 67% in the SFC group, the value being significantly different between the two groups ($p < 0.01$).

Discussion

To our knowledge, this is the first study to compare the treatment with LABA alone and with combination of inhaled corticosteroid and SAL for CVA. Our present study on patients with CVA showed that treatment with SFC and SAL alone for 12 weeks each provided a decrease in cough symptom scores. CVA is essentially an occult form of asthma,

Figure 5. Number of eosinophils in blood (left panel, $n = 18$ –22 for each point) and induced sputum (right panel, $n = 14$ –18 for each point) in patients with CVA. Values are mean $\pm$ SE. * $p < 0.05$, significantly different from corresponding values for SAL.

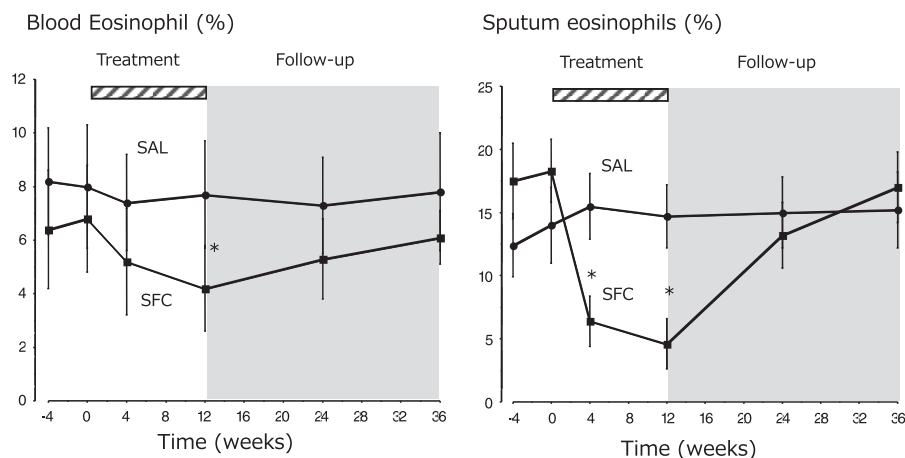


Figure 6. Concentration of ECP in serum (left panel, $n = 17$ –22 for each point) and induced sputum (right panel, $n = 13$ –17 for each point) in patients with CVA. Values are mean $\pm$ SE. * $p < 0.05$, significantly different from corresponding values for SAL.

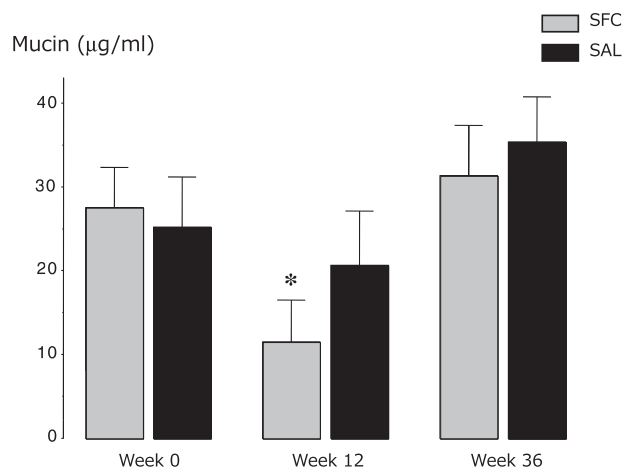
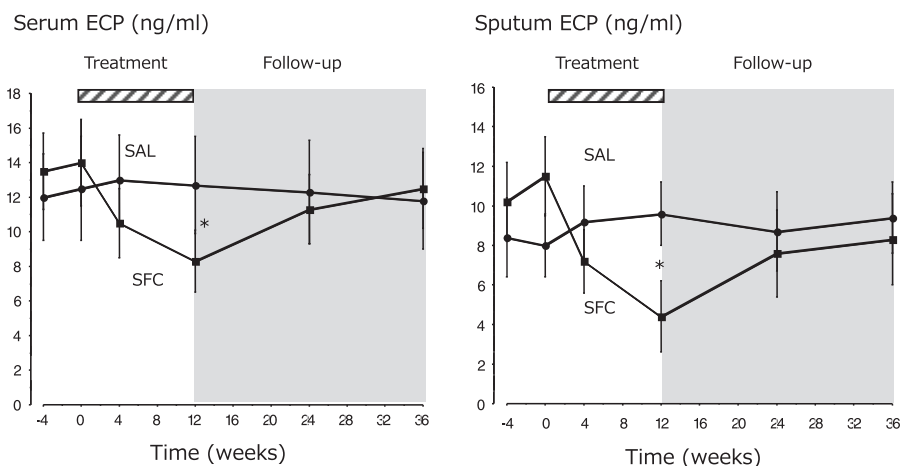


Figure 7. Concentrations of mucin in induced sputum in patients with CVA at week 12 (end of treatment phase) and at week 36 (end of follow-up phase). Values are mean $\pm$ SE; $n = 13$ –17 for each bar. * $p < 0.05$, significantly different from the values at week 0.

in which the only symptom is cough without showing dyspnea or wheezing, and cough in CVA is presumably caused by subclinically mild airway spasm, and the response to bronchodilator is thus useful for diagnosis of the disease [11,12]. However, it should be noted that LABA is no longer available in US and Europe as single agent therapy for asthma.

It has been accepted that CVA is similar to typical asthma, in terms of eosinophilic airway inflammation and bronchial hyperresponsiveness, and some patients with CVA progress to typical asthma. Niimi et al. [13] showed the infiltration of eosinophils and the increased thickness of basement membrane in the airway mucosa of patients with CVA, suggesting that the process of airway remodeling may be ongoing. Thus, anti-inflammatory agents are effective in the treatment of CVA. The current guidelines strongly recommend anti-inflammatory agents including inhaled corticosteroid for the first line therapeutic approach. For these reasons, we hypothesized that combination therapy with inhaled corticosteroid and LABA may provide more favorable effects. Therefore, although such a combination therapy is not recommended by guidelines for the treatment of CVA, we tested the clinical efficacy of SFC. In the present study, daily dose of salmeterol was 50 μ g in the SFC group and 100 μ g in the SAL group, and we found that the SFC group showed a greater improvement in cough symptom score and FEV₁ compared with SAL group, in spite of a half dose of β_2 -agonist.

There is ample evidence that eosinophilic airway inflammation plays an important role in the pathophysiology of CVA as with classic asthma. It has been shown that number of eosinophils and concentrations of ECP are increased in sputum, bronchoalveolar lavage fluid and bronchial mucosa in patients with CVA [3]. In agreement with these studies, our

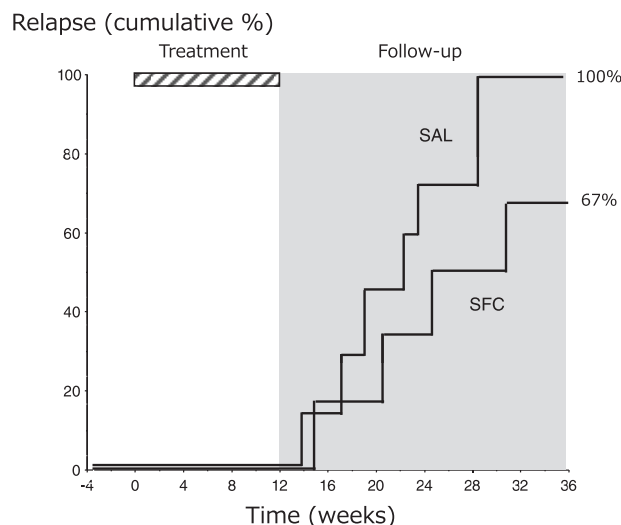


Figure 8. Kaplan–Meier analysis of relapse rate in the SFC ($n=21$) group and the SAL ($n=22$) groups throughout the trial.

patients had elevated eosinophil counts and ECP contents in the peripheral blood and induced sputum. Liu and colleagues [12] reported that compared with control group, CVA group was found to have higher baseline levels of IL-5 and eosinophils in induced sputum, and the number of eosinophils significantly decreased after treatment with inhaled corticosteroid for 6 months in CVA patients. In addition, Kim et al. [14] found that higher percentage of sputum eosinophils in CVA patients was associated with the development of classic asthma at follow-up, and Fujimura et al. [15] reported that treatment with long-term inhaled corticosteroid prevented the development of classic asthma from CVA and reduced bronchial responsiveness. Recently, Tamaoki et al. [16] showed that pranlukast, a leukotriene receptor antagonist, caused improvements in cough symptoms and eosinophilic airway inflammation to a greater extent than did salmeterol in patients with CVA. Taken together, anti-inflammatory therapy seems important not only for reduction of cough symptoms but also for prevention of progression to typical asthma in the future.

Airway mucus hypersecretion is one of the characteristic features of asthma [17,18], and it is known that mucin concentration in the induced sputum is higher in patients with CVA than healthy subjects [19]. In the present study, sputum mucin contents decreased after the treatment with SFC, but not by SAL alone. Thus, this finding is likely derived from anti-inflammatory effect of the corticosteroid fluticasone. However, the role of hypersecretion of airway mucin in the pathogenesis of CVA requires further studies.

There have been arguments as to whether maintenance therapy with inhaled corticosteroid can be discontinued in patients with mild asthma [20,21], and the effect of the discontinuation has not been studied in patients with CVA. We found that after stopping of the treatment for 24 weeks, cough scores increased and FEV₁ decreased toward the baseline levels in both treatment groups. Furthermore, eosinophilic inflammation and airway mucus hypersecretion were also aggravated, and the number of patients with relapse of the disease increased. However, the rate of relapse was lower in the SFC group than in the SAL group, suggesting

that an anti-inflammatory drug might play a role in preventing the relapse even after discontinuation of the therapy.

Conclusion

We found that maintenance therapy with a combination of inhaled corticosteroid and long-acting β_2 -agonist provided improvements in cough symptoms, pulmonary function and airway inflammation more effectively than did long-acting β_2 -agonist alone, and that discontinuation of the therapy caused worsening of the disease. Therefore, anti-inflammatory therapy with corticosteroid is important in the management of CVA and stopping or interrupting such therapy may not be advisable. However, long-term study is needed to elucidate its safety, and whether prolonged anti-inflammatory effect can actually prevent the development of the disease, including airway remodeling and it remains uncertain progressive loss of pulmonary function, later in life.

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Declarations of interest

The authors do not have any declarations of interest.

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